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LESIONS OF THE BRACHIAL PLEXUS ASSOCIATED WITH RUDIMENTARY RIBS.

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INTRODUCTORY.

RUDIMENTARY ribs at the upper thoracic operculum have for centuries attracted the attention of anatomists. According to Keen [12], whose paper should be referred to for the historical aspect of the subject, the earliest account of such an anomaly is that given by Hunauld in 1740, and many descriptions of sporadic specimens are scattered throughout the old anatomical and surgical literature. The advent of evolutionary ideas drew to them the attention of morphologists, some of whom attempted to show that the "general shortening of the thoracic region, which is at work throughout the mammalian series, was evidenced as a distinct and ordered evolutionary process from ape to man" (Wood Jones) [9]. The studies of Dwight [5] and others failed to confirm this view, and Dwight concluded that these costal and vertebral anomalies are "merely variations round a mean, which for want of a better word we must call accidental."

Were it not for the correlated abnormalities of the soft parts, and the symptoms which may arise by reason of this association, these rudimentary osseous structures might have failed to attain a position of any practical interest. When aneurysms were common and occupied much of the surgeon's attention, an accessory rib was regarded as a possible cause of that condition, or as a convenient *point d'appui* for pressure in its treatment. It was also recognized that such a rib might give rise to difficulty in diagnosis. Thus Paget [17] wrote: "The imitation of subclavian aneurysm is made more marked when a nervously pulsating subclavian artery lies upon a cervical rib." It is only comparatively recently that the importance of these anomalies from the neurological point of view has been fully recognized.

Patients suffering from symptoms due to a rudimentary rib constitute a clinical group of not inconsiderable size, to which we are in a position to transfer a number of cases from amongst those bearing such "diagnostic" labels as brachial neuritis, brachial neuralgia, uniradicular palsy, progressive muscular atrophy, writer's cramp, occupation neurosis and symmetrical atrophy of the hands. Thus Farquhar Buzzard [3] in 1902 described six cases of nerve-root lesion under the title of "Uniradicular Palsies of the Brachial Plexus." A review of the clear and accurate account of these cases cannot but convince one that four were instances of the lesion which would now be ascribed to "cervical rib." Similarly, as pointed out by Bramwell and Dykes [2], Lewis Jones [11] reviewed in 1908 a group of cases to which he had drawn attention in 1893 under the title of "Symmetrical Atrophy affecting the hands in young people," and found a well-marked cervical rib to exist in no fewer than ten out of fourteen patients of that group.

Relation between Costal Anomalies and the Nerves constituting the Brachial Plexus.

Wood Jones [9] has demonstrated the fact that costal anomalies are associated, as he believes causally, with variations in the constitution of the brachial plexus. He believes that the development of ribs both in the cervical and lumbar regions is arrested at the points where the nerves, taking an oblique course in order to reach the limbs, cross the primitive mesoblastic costal elements, thus giving rise to the "ribless neck and waist." The first indication of this interrelation is to be found in the neural grooves upon the first rib. The first thoracic root[1] (or the lowest cord of the brachial plexus resulting from its junction with the eighth cervical) in passing to the axilla causes, by pressure, the groove upon the first rib which, from being supposed to lodge the subclavian artery, is commonly known as the sulcus subclaviæ; this groove he consequently prefers to call the sulcus nervi brachialis. When the first thoracic root is very large, the groove may be so strongly marked that the rib is actually bent downwards at this point. When a large part of the second thoracic nerve goes to the brachial plexus, the first rib may actually be deficient, and may be either continued on to the sternum as a fibrous cord, or pressed down upon and fused with the second rib so as to constitute a "bicipital rib."

[1] Where the term "root" occurs, it indicates that part of the anterior primary division of the spinal nerve which enters the brachial plexus.

A brachial plexus so constituted is a post-fixed plexus. The conclusion is therefore that the more post-fixed the plexus, the more likely is the first rib to be ill developed or abbreviated. Conversely, a pre-fixed plexus is likely to be associated with an abnormal development of the costal element of the seventh cervical vertebra, and there are many facts which lend support to this view. It is true however only within certain limits. Wingate Todd [22], as the result of his observations, concludes that "cervical ribs may be present in cases where the composition of the brachial plexus is normal" and that "the disposition of the nerve trunks alone is insufficient in many cases to account for the presence and length of rudimentary ribs." During many of my operations I have attempted to make a careful examination of the plexus so as to determine its composition. On one occasion when I could find no contribution from the first thoracic nerve, I stimulated the eighth cervical root and caused contraction of all the intrinsic muscles of the hand. In other instances, however, the contribution from the first thoracic nerve has been evident, and apparently of normal size. Similar discrepancies may be noted in the descriptions of dissections which are to be found scattered throughout anatomical literature. In this connection the description given by M. F. Lucas [14] of the composition of the brachial plexus in two dissecting-room subjects is particularly interesting. In a female subject the left rib, 6 cm. long, was attached by a short fibrous band to the medial border of the first rib, and was grooved by the lowest and middle trunks of the plexus. The fourth cervical nerve contributed to this plexus, which was only slightly prefixed. On the right side the cervical rib was only half as long, and here the fourth cervical nerve made no contribution to the plexus, whilst the contribution of the first thoracic nerve was appreciably larger than on the other side. In a male subject, each cervical rib was a little over 4 cm. long, and in both cases the composition of the brachial plexus was normal. Hertslet and Keith [7] give a drawing showing side by side, for comparison, one thorax with a rudimentary first thoracic rib and another with a cervical rib. The first is associated with a postfixed plexus and the second with a prefixed plexus. In the case of the rudimentary thoracic rib a large part of the second thoracic nerve joins the whole of the first thoracic, the combined nerve passing over the bony part of the rib. In the case of the cervical rib, a small branch from the first thoracic nerve passes up to join the eighth cervical, the combined nerve passing over the bony part of the rib. This plexus receives a large branch from the fourth cervical

nerve. Arbuthnot Lane recorded a case of rudimentary first thoracic rib with a definitely postfixed plexus. Describing a specimen of cervical rib he notes that the "firm tendinous cord" which continues the line of the cervical rib is attached to the upper margin of the first thoracic rib and its cartilage.

It seems quite clear therefore that although, generally speaking, some prefixation of the plexus is usually to be found associated with cervical ribs, and some degree of postfixation with abnormal first thoracic ribs, yet the relationship is by no means constant. Nor does the form and size of the abnormal rib appear to bear any constant relation to the composition of the plexus.

Were the plexus always prefixed for a complete segment when a well developed cervical rib is present, we should expect, other things being equal, that no symptoms would occur. On the other hand, a large contribution from the first thoracic nerve, by passing over the accessory rib or its fibrous continuation, would be more exposed to injury, and symptoms would be more likely to arise. Prefixation of the plexus would thus be an advantage in the presence of a cervical rib.

Classification of Cervical Ribs.

The classification of Gruber, quoted by Keen, is as follows:—

"*First degree*, a very slight increase of the costal process, not reaching beyond the true transverse process. *Second*, a rib protruding beyond the transverse process to a moderate extent and ending either free in the tissues or attached in some way to the first thoracic rib. *Third*, a still further degree of development in which the cervical rib extends for a considerable distance toward or even to the cartilage of the first thoracic rib, possesses a complete body, and is united directly or by means of a ligament with the cartilage of the first rib. *Fourth*, a complete cervical rib uniting at the anterior extremity with the cartilage of the first rib through which it reaches the manubrium."

This however does not embrace all the forms which may be met with, and takes no account of whether or not the rib is jointed to, and therefore to some extent movable upon, the seventh cervical vertebra. It therefore requires amplification.

The actual length and shape of the bony portion of the rib does not seem to have any great clinical significance; its direction, on the other hand, is important, as was first pointed out by Thorburn [21]. This fact is well illustrated by a remarkable case of my own (Case 31).

where the rib, after subperiosteal resection, was reproduced, but, being moulded during its reincarnation in a direction less at variance with that of the nerves, the symptoms previously present did not reappear. A somewhat similar case by Weber is quoted by Hinds Howell [8]. Subperiosteal resection of a cervical rib was followed by regression of the symptoms which, however, reappeared with the re-formation of the bone. Subsequent removal resulted in recovery.

The mobility of the rudimentary rib may also influence the symptoms, so that the jointed rib, whatever its length, deserves separate notice.

The types which I recognize are as follows :—

(1) An exaggerated costal process of the seventh cervical vertebra, not jointed to but fused with the transverse process, and continued forwards and downwards as a fibrous band to be attached to the first thoracic rib behind the scalene tubercle.

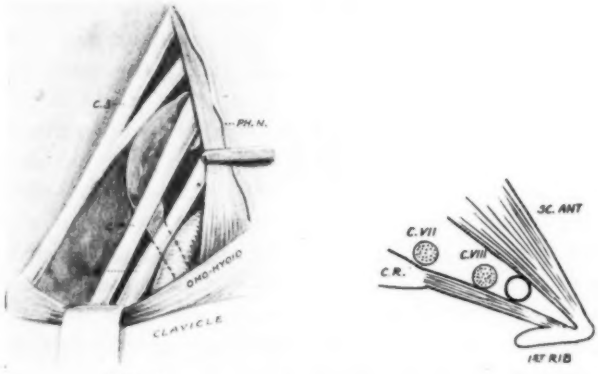


FIG. 1.

Fig. 1 represents an example of Type 1, where the bony rib is unusually long for a non-articulated rib. The diagram alongside indicates in section the relation of the nerves and artery to the abnormal costal elements.

(2) A short rib, articulated to the seventh cervical vertebra by costo-central and costo-transverse joints, and continued onwards as a fibrous band to be attached to the first rib as in type 1.

(3) A jointed rib of sufficient length to carry the eighth root upon its bony portion, and attached by a fibrous band to the first rib.

(4) A jointed rib of which the anterior extremity makes contact with the first thoracic rib, the two being either fused, or united by an irregular articulation.

(5) A rudimentary first thoracic rib, the anterior fibrous portion of which is attached to the sternum, usually by a rudimentary costal cartilage.

Varieties doubtless exist amongst these types. This is exemplified by the following instance which I am unable to place in the foregoing classification (fig. 18). *Case* 28: The rib was articulated both with the body and transverse process of the seventh cervical vertebra. The seventh and eighth cervical roots lay upon the bony rib, being separated by a well-marked ridge. The anterior extremity was continued on towards the anterior end of the first thoracic rib, passing in front both of the subclavian artery and the first thoracic nerve. Hinds Howell [8] mentions a similar case operated upon by Rawling in which the rib projected between the eighth cervical and first thoracic roots which united beyond it.

Relation of the Spinal Nerves to Cervical Ribs.

The relation of the roots of the brachial plexus to the various types of rudimentary ribs appears to be fairly constant, and is indicated in the diagrams. The observations made during the course of an operation cannot however be as accurate as those made in the dissecting room, and the point least easily ascertained by operative dissection is the size of that portion of the first thoracic nerve which enters the plexus, and its exact relationship to the abnormal costal element. One cannot always determine therefore whether the lowest nerve seen is the eighth cervical alone, or the combined trunk of the eighth cervical and first thoracic roots. It may however be stated quite confidently that the commonest arrangement is for the seventh root to lie upon the bony part of the cervical rib, and for the eighth root (or the lowest cord of the plexus) to be carried upon the fibrous portion. Further, my observations have convinced me that, whilst the contribution of the first thoracic nerve to the plexus may be of considerable size, it is usually small and may even be absent. This confirms the view that when a cervical rib exists the plexus tends to be of the prefixed type. It is certainly not true however to say that the better developed the cervical rib the more prefixed is the plexus, or vice versa. A rudimentary first thoracic rib is a much rarer anomaly than a cervical rib, but it seems to be an established fact that in such cases the plexus tends to be of the postfixed type. This is in harmony with the observation of Wilfred Harris [6] that the postfixed is not so common as the prefixed type in man.

The Sympathetic Nerves.

The main sympathetic nerve supply to the upper limb comes from the inferior cervical and first thoracic ganglia, usually by two trunks which enter the first thoracic and eighth cervical nerves close to their foramina of exit from the vertebral column. A communication, stated by Cunningham to occur in 70 per cent. of cases, from the second thoracic nerve joins the first thoracic, and contains sympathetic fibres. Wingate Todd [22] has given a diagram of this arrangement, and has pointed out how the sympathetic nerves to the upper limb may be subjected to injury in the presence of a cervical rib.

Dissections made by Professor F. G. Parsons and myself show the sympathetic branches entering the brachial nerves (fig. 2). I have

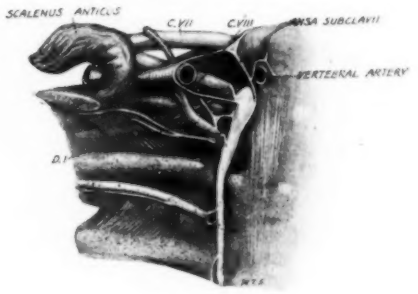


Fig. 2.—From a dissection by F. G. Parsons, showing sympathetic branches to the brachial plexus.

attempted to trace these nerves after their incorporation with the main trunks. Dr. W. Penfield has made serial sections which show that bundles both of small medullated and of non-medullated fibres tend to lie, at first at any rate, in the periphery of the mixed nerve. It may be that this arrangement is very variable, and that in those patients who exhibit well-marked vasomotor symptoms the sympathetic fibres are specially exposed to injury from their superficial position. As regards oculo-pupillary symptoms, the only instance which I have encountered where such were present occurred in a woman 42 years of age. It was noted that the right pupil (the affected side) was smaller than the left, and that the right palpebral fissure was sometimes wider than the left. When seen six years after operation no such symptoms could be detected, and the arm had completely recovered.

Thorburn [21] states that he never saw oculo-pupillary signs, and that the only case in Schönbeck's series had co-existent syringomyelia.

The Subclavian Vessels.

The height to which the subclavian artery rises in the neck varies considerably in normal individuals, and is naturally affected by the position of the shoulder. Many patients with symptoms due to cervical rib are "bottle necked," and the droop of the shoulders tends to exaggerate the height to which the artery rises above the clavicle. In some recorded instances the artery has been found passing over the accessory rib. I have not encountered an example of this condition amongst the patients upon whom I have operated. The only case in which I have seen the artery passing over an abnormal rib was an example of rudimentary first thoracic rib. In almost all my cases the artery has been found either lying upon the first thoracic rib, or just held off from it by the fibrous band. In two instances a very large transversalis colli or suprascapular artery has been found lying upon and grooving the cervical rib. The pulsations of this vessel had been noted before operation, and might easily have been mistaken for those of the subclavian artery.

The varying relation of the artery to abnormal ribs described by Wingate Todd [22] corresponds closely with my own observations.

In a recent case of my own, a well marked example of Type 4, the course of the subclavian artery was so peculiar as to deserve special mention (fig. 3). A large accessory rib, which formed a remarkable prominence in the supraclavicular fossa, was joined by an irregular articulation with a mass of bone upon the upper surface of the first rib. The subclavian artery rose high in the neck to the inner side of the accessory rib, and then, bending downwards, grooved the inner aspect of the mass of bone formed partly from the cervical rib and partly from the first thoracic rib. It then turned outwards just below the bony mass, to reach the axilla. There was no contribution to the plexus from the first thoracic nerve. The lowest cord and the subclavian artery were thus separated by a mass of bone, and over this there had developed a well-marked synovial bursa.

A number of cases have been reported as having had aneurysmal enlargements upon the artery. The subject is fully discussed by Keen [12] and need not be further considered here. At most of my operations the artery has been carefully observed, and in only two was anything resembling a dilatation seen. Both were examples of Type 4,

the cervical rib being attached to the first thoracic rib by a mass of bone against which the artery lay. In one the artery was dilated proximal to the mass, and in the other a fusiform dilatation existed at the point of contact. In the latter no radial pulse could be felt; in the former the pulse disappeared with the arm in the dependent position. In a third case, belonging to the same type, the artery was definitely narrowed at the point where it crossed the bony mass resulting from the fusion of the cervical with the thoracic rib. In this patient no radial pulse could be felt in any position of the limb; a systolic bruit was to be heard, and a thrill could be felt, above the clavicle. The absence of the radial pulse in the dependent arm is but an exaggeration of a common phenomenon in cases of cervical rib.

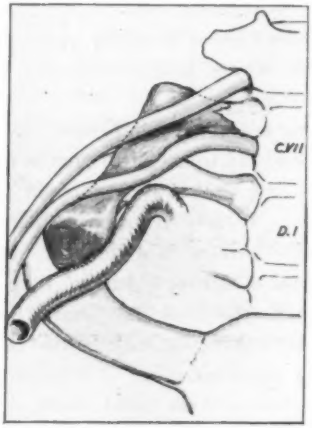


FIG. 3 is an example of Type 4, with a definitely prefixed plexus, and the subclavian artery in peculiar relationship.

When the arm is hanging by the side, the least downward traction will often cause the radial pulse to disappear. In many instances of bilateral cervical rib I have noted that the radial pulse can more easily be made to cease by this means on the side of the most pronounced nerve symptoms. Doubtless the artery is, in these cases, subjected to the same mechanical strains as is the lowest cord of the brachial plexus. Similarly, a systolic murmur, not conducted down the arm, can sometimes be heard just above the clavicle, and can be made to vary with the position of the arm. The subject of arterial thrombosis and gangrene of the fingers is also fully discussed in Keen's

paper, to which reference should be made. No such case has come under my own observation. "Vascular symptoms" have, in my patients, always been due to vasomotor disturbances.

The subclavian vein is rarely obstructed, and indeed its position is such that it can scarcely come into relation with any part of any cervical rib. Thorburn mentions one case in which he believed that the œdema might have been due to pressure on the subclavian vein.

Causation of the Symptoms.

The factors which determine the onset of symptoms in persons with cervical ribs are so excellently presented in a recent paper by Bramwell and Dykes [2] that a full discussion is unnecessary here.

That the lesion is traumatic cannot be doubted. In the cases of sudden onset of symptoms some definite strain has occurred, such as lifting a heavy weight, which would naturally bring nerve and "rib" into sudden and violent contact.

When the symptoms are of gradual onset the damage is, I believe, produced by the continual friction of the nerves against the non-ossified costal process, caused by the movements of the arm and by the respiratory movements. I have frequently been able to demonstrate, during an operation, the manner in which the nerve is pushed upwards and rolled over as the band tightens during inspiration and in certain positions of the arm. Further, it can easily be seen that as soon as the band is excised the nerve at once sinks to a lower level in the wound and is relieved of all tension. I believe the mechanism to be commonly as follows: The fibrous band, springing from the costal process of the seventh cervical vertebra, is usually attached to the upper surface of the first thoracic rib behind the axis of movement of that rib. As the anterior end of the rib rises in inspiration, the posterior part tends to sink, so that the band is made taut, and comes into harmful contact with the nerve which lies against it. Thomas and Cushing [19], in 1903, suggested that the fibrous band was the cause of the symptoms. Here "the lowest cord of the plexus was compressed by a dense fibrous band which passed from the tip of the rudimentary rib under the plexus to its point of attachment to the first thoracic rib. The band therefore over which the lowest cord of the plexus arched at rather an acute angle was the offending agent rather than the bony projection itself."

Whether any gross histological changes occur in the damaged nerve,

such as can be demonstrated in an ulnar nerve similarly affected by rolling movements over an abnormal humeral condyle, I have had no opportunity of ascertaining, but one would naturally suppose that such changes would occur, and that they would be the more pronounced the longer the symptoms had persisted. This supposition is supported by the fact that the rapidity and degree of recovery after operation are to a large extent related to the previous duration of the symptoms. On the other hand, I have never encountered any instance of palpable thickening, nor have I seen any naked-eye evidence of damage, except in one case in which a distinct groove marked the nerve at the point where it had been in contact with the band.

I have now operated upon sixty-five patients for the relief of symptoms due to a "cervical rib." Whilst the ribs were always bilateral, they were not invariably symmetrical, and when any conspicuous difference in size existed the symptoms were most frequently worse on the side of the smaller rib. The right arm was wholly or chiefly affected in thirty-three patients and the left in twenty-four, whilst eight patients presented well marked bilateral symptoms.

The age and sex incidence in my cases conform with those noted by other observers. Of sixty-two patients the average age was thirty-five; fifty-five were females and seven males.

With the exception of three school children (aged respectively 12, 13, and 15), one artist, and one patient who might be classed amongst the "idle rich," all were engaged in active and often strenuous pursuits. Amongst the males there were two painters, one medical practitioner, one soldier, and one stoker. Of the females there were thirty-two employed in domestic work, five clerks, five nurses, three seamstresses, two pianists, two shop assistants, two telegraphists, one typist, one letter sorter, one teacher, and one milk-carrier.

Symptomatology.

The symptoms which may be caused by a cervical rib are well known. Pain, paræsthesia, disorders of circulation, affections of cutaneous and other forms of sensation, weakness, wasting, and alteration of electrical reactions, occur in varying combination and in varying degree in individual cases. These symptoms may be grouped into those of damage to:—

(1) Somatic afferent fibres, namely, neuralgic pain, and disturbances of cutaneous and deep sensibility.

(2) Somatic efferent fibres, namely, weakness, wasting and alteration of electrical excitability in the affected muscles.

(3) Sympathetic fibres, namely, circulatory disturbances (coldness, cyanosis, œdema) and certain paræsthesiæ (tingling, numbness, and feelings of coldness or swelling).

Counting each case with bilateral symptoms as two, the order of frequency of the symptoms for which the patients seek relief is (in fifty-eight cases) as follows :—

(1)	Weakness	48 = 79	per cent.
(2)	Aching or paroxysmal pain	42 = 72	,,
(3)	Paræsthesia	24 = 39	,,

Muscular wasting was evident in forty-three (72 per cent.), objective sensory loss in twenty (34 per cent.), and signs of vasomotor disturbances in seven (12 per cent.).

The "weakness" of which so many patients complain is sometimes described as "clumsiness," or inability to perform the finer acts demanded of the hand, especially after the hand has been in use for some time. Thus writing, sewing, typewriting, and piano playing may be rendered difficult or impossible. This symptom is often complained of by those with no visible muscular wasting, and is presumably dependent upon a disturbance of deep sensibility. In early cases it is inconstant, only occurs as the result of exertion, and quickly passes off with rest. We find that sixteen out of fifty patients were engaged in pursuits requiring the constant use of the hands for fine and specialized movements. We may no doubt add to these a certain number of the patients engaged in domestic work, for much needlework falls to the lot of a good many of them.

The Affected Muscles.

Kinnier Wilson [24] was the first to draw attention to the fact that some patients with cervical rib exhibit a characteristic peculiarity in the muscular wasting. This peculiarity consists in the picking out of abductor brevis and opponens pollicis, the other thenar muscles being relatively or absolutely unaffected. He concludes that the thenar muscles derive their nerve supply from two roots, namely, the abductor and opponens from the seventh and the flexor brevis pollicis from the eighth cervical.

With a normal arrangement of the brachial plexus the hypothenar muscles derive their nerve supply from the first thoracic root, the interossei chiefly from the eighth cervical, and the superficial flexor

muscles of the forearm from the sixth cervical. In the thirty-two cases of my series belonging to Types 1 and 2 which exhibited muscular wasting, all the intrinsic muscles of the hand and the superficial flexors of the forearm were affected six times; all the intrinsics of the hand (without forearm involvement) fourteen times; whilst in twelve instances the muscles chiefly affected were the abductor and opponens pollicis. In terms of normal roots this would mean involvement of—

C6, 7, 8 and T1 in six,
C7, 8, and T1 in fourteen,
and C7 and 8 in twelve.

Thus C6 would be involved in six, and T1 would be left out in twelve, C7 and C8 being affected in all. We are, however, dealing with plexuses of varying composition, but with a tendency to prefixation, in which the contribution from first thoracic nerve is small or absent. The muscles of the hand are therefore in these cases chiefly supplied by the eighth and seventh roots, which are those most exposed to the traumatism of the commonest variety of cervical rib.

Theodore Thompson [20], commenting upon the difficulty of understanding why a seventh cervical rib should cause symptoms referable to the first thoracic root, called attention to the varying constitution of the lowest cord of the plexus associated with cervical ribs.

The Sensory Changes.

In all cases cutaneous sensibility to cotton wool and to pin-prick has been carefully tested. Unfortunately the other forms of sensibility have been too rarely investigated with accuracy to permit any general statement being made, but impairment both of thermal and of postural sensibility have been noted several times, in addition to those of pain and touch.

In 60 per cent. of my cases no alteration of sensibility either to cotton wool or to pin-prick was detected. Whether more accurate testing might have revealed some abnormality it is impossible to say, but at any rate it can be stated definitely that in at least half the cases which have come under my own observation any sensory changes which may have existed were too slight to be detected by the ordinary clinical means of examination.

In twenty cases carefully charted, there was dulling of sensibility to pin-prick and cotton wool, distributed regionally as follows:—

Ulnar border of arm, forearm and hand	3
,, ,, forearm and hand	4
,, ,, forearm	3
,, ,, hand	5
Radial border of arm and forearm	1
,, ,, forearm and hand	2
,, ,, hand	2

According to the commonly accepted delimitation of root areas, we should have concluded that the roots most often affected were, in order of frequency, the first thoracic, the seventh cervical, the second thoracic, and the sixth cervical, whilst the eighth cervical nearly always escaped.

Let us however review the forty-four cases belonging to Types 1 and 2, where the seventh root rests upon the bony part of the rib and the eighth (or lowest cord) is carried upon the fibrous band. In only fourteen of these was any sensory change detected, and in twelve of them its distribution corresponded with the usual distribution of the first thoracic root—in two with that of the seventh cervical. We are not however dealing with a normal plexus, but with a plexus of the prefixed type in which the area usually supplied by the first thoracic root tends to be supplied by the eighth cervical, namely, that which is most exposed to the traumatism of the fibrous band. In the majority of cases therefore the distribution of the cutaneous alteration of sensibility comes into line with the anatomical arrangement observed at operation.

In this connection attention may be called to two particular cases. In one (Case 12), the area of diminished sensibility to pinprick and cotton wool embraced only the thumb and the terminal phalanges of the index and middle fingers, whilst the only muscle affected was abductor brevis pollicis. Here the eighth cervical root passed over the tight band, whilst the first thoracic, passing beneath the band, escaped injury. In the second case (Case 49) the area of diminished cutaneous sensibility embraced the radial half of the forearm, both behind and in front, together with the thumb, index, and middle fingers; there was no muscular wasting. In this case the first thoracic nerve made no contribution to the plexus. It cannot be said that these cases furnish, either from the distribution of the sensory changes, or the muscles affected, any reliable information of morphological value regarding the normal distribution of the roots of the brachial plexus. Not only is the degree of shifting of the plexus upwards or downwards upon the cord variable, but the position which the different bundles of fibres occupy in the individual spinal nerves is probably subject to much variation.

The bundles which are situated nearest the surface of the nerve at the point of contact with the abnormal rib would presumably suffer most severely.

A recognition of the usual relation of these variable plexuses with the various kinds of cervical rib is, however, important from a practical point of view. In 1903 Edwin Bramwell [1] reported a case the salient features of which were as follows: pain down the inner side of right forearm for about three years; gradual loss of power in the hand, with cold feeling, for about twelve months; wasting of thenar and hypothenar muscles together with pronounced weakness of the flexors of the fingers; an area of impaired sensibility on the ulnar side of the forearm from just above the elbow down to the wrist. Having made a diagnosis of a lesion of the first thoracic root before its junction with the eighth cervical, he writes: "It is interesting to note the intimate relation of the first dorsal nerve-root to the sharp internal border of the first rib. Such a relation can hardly fail to predispose this root in an especial manner to traumatism." The suggestion of a first rib, rather than a cervical rib, being the cause of the symptoms in a case of this character, thus made for the first time, has been acted upon, and in several cases Stiles has removed a portion of the first rib, with excellent results. Similar cases are recorded by Morley [15], Murphy [16] and others. Stopford and Telford [18] have fully recorded and discussed seven examples of a similar nature. In their first case "a very large contribution from the first dorsal root was found ascending in a deep groove on the inner border of the first rib to join the eighth cervical root." There was a small cervical rib on the other side, but none on the affected side. In another of their cases "the contribution from the first dorsal segment of the cord was unusually large." They express the opinion that "a predisposing cause seems to be the anatomical relation of the nerve trunk and the rib, when the bone is bevelled by a trunk which receives a large contribution from the upper two dorsal roots."

In the light of these reports I have reviewed my own cases of cervical rib. Amongst them are several cases presenting symptoms of lesion of the first thoracic root in which the radiographic evidence of cervical rib was negative. In one such instance the note made at the operation states that a strong fibrous band, over which the eighth root passed, tightened in a very conspicuous manner with each inspiration, and that on its detachment from the tip of the seventh cervical costal process it was immediately pulled downwards for fully half an inch.

This patient was cured and remains well after an interval of nine years. I believe that the same good result would have followed Stiles' operation of removal of a portion of the first thoracic rib, carrying with it the lower attachment of the non-ossified " cervical rib." I believe, too, that in some cases the more complete relief of tension which Stiles' operation affords would probably render it the procedure of choice, and I am inclined to think that some of my failures might for the same reason have been successes had the larger operation been done. Stiles' operation, however, is designed for relieving the first thoracic root from the pressure of a normal first thoracic rib. In such cases one would expect that the plexus would tend to be to some extent postfixed, and the cases would fall into a class approximating to that which is characterized by a rudimentary first thoracic rib with a frankly postfixed plexus.

Treatment.

All the symptoms which may be caused by a cervical rib are capable of relief or cure. It must not be forgotten that these are common anomalies, and just as cervical ribs frequently exist without causing any symptoms whatever, so also they are likely to be found in patients presenting similar symptoms due to some totally different cause. Such indeed is the case, and unless the greatest care is exercised there is considerable risk that futile operations may be performed on patients with syringomyelia, progressive muscular atrophy, toxic neuritis, and other conditions wholly unconnected with the co-existent cervical rib. On the other hand there is perhaps even more risk that patients whose symptoms are due to such a costal anomaly may be denied the prospect of relief on account of failure to recognize the fact that " neuritis," " brachial neuralgia," and certain occupational disabilities are so often directly dependent upon rib-pressure. In cases of real doubt it is certainly legitimate to afford the chance of relief offered by an operation which, gently and carefully performed, is almost entirely free from risk.

Operation is not called for in all cases. In some a change of occupation is sufficient; in others a greater use of the other arm to relieve the affected side. The wearing of a sling is often beneficial. Yet again, the development of the muscles which support the shoulders by massage, muscle-training, and other means is a useful line of treatment. Patients however who are obliged to continue following certain occupations, and who cannot give up the time necessary for muscle

training, should be submitted to operation. Other forms of treatment, such as those mentioned, may be required in addition.

The details of the surgical operation need not be given here. Suffice it to say that its object is not merely to remove an abnormal bone, but to divide or excise any non-bony fibrous structure against which the nerves are being damaged. In one case, for example, a clean subperiosteal resection had no effect upon the symptoms; subsequent resection of the periosteum gave complete relief.

Gentleness of manipulation, clean dissection, and a bloodless operative field are essential, as well as an accurate knowledge of the anatomical relations of the parts concerned. The importance of the last-named point is well brought out by Coote [4] in the somewhat quaint account of the first recorded case of an operation for cervical rib which I have been able to find.

Results of Operation.

In my series there has been no fatality, and in no instance has any wound infection occurred. In only two instances did any ill-effect follow the operation. In one a severe organic monoplegia developed, which only cleared up after many months. In another a hysterical paralysis occurred, for which treatment was refused, and the patient was lost sight of.

The results are most fairly presented in the brief notes to be found in the tables, for each of the most prominent group of symptoms deserves separate notice. These tables were prepared before the War, and it has been interesting to note that, in reviewing the cases after a further long period, some which were previously entered as "relieved" have had to be transferred to the "cured" column, whilst others, where relapse has occurred, have had to be transferred to the group marked "relieved."

Pain.

As regards pain, twenty-seven patients have been followed for a sufficiently long period to judge of the result; nineteen of them are cured and the rest very considerably relieved. Where pain is the predominant symptom it may safely be predicted that the result of operation will be gratifying, and that the relief of pain will usually be immediate and permanent.

RESULT OF OPERATION AS REGARDS PAIN.

Cured.

Case 2.—Female, aged 38, housekeeper. History five years. Constant aching along ulnar side of whole arm and shoulder. After eight months, pain only in opposite arm. After seven years, "pain gone but fingers drawn."

Case 5.—Female, aged 51, housework. History three years. Pain in right shoulder and occasional neuralgic pain along ulnar border of forearm and hand; also wasting and vasomotor symptoms. Immediate relief of pain. Ten months later no pain, but still some weakness. Seven years later, remains free from pain; "constantly using my hands from 7 a.m. to 9 p.m."

Case 7.—Female, aged 36, housework. History five months. Neuralgic pain in shoulder and inner side of arm, forearm and hand; also weakness and wasting. Immediate relief of all pain. Remains well and at work six months later. Seven years later, "occasional pain in both arms."

Case 8.—Female, aged 50, housework. *Left side:* History six months. Neuralgic pain in shoulder, inner side of arm, forearm and hand, increased by work; also weakness. Ten months later no pain. Occupation unchanged. *Right side:* Symptoms exactly similar to those of left side. Immediate relief. After eight months, completely free from pain. After six years, right completely free; left free until two years ago, when occasional pain after unusual exertion.

Case 11.—Female, aged 52, housework. History three years. Aching in shoulder and neuralgic pain in thumb. Immediate relief of pain. Remains free from pain after ten years.

Case 16.—Female, aged 22, clerk. *Left side:* History two years. Pain in shoulder, inner side of elbow and inner fingers. Immediate and complete relief of pain. Remains well five years later. No change of occupation. *Right side:* History four months. Pain in shoulder, inner side of forearm and wrist. Immediate relief of pain. Remains free five years later.

Case 21.—Female, aged 25, housework. History two and a half years. Also vasomotor symptoms. Aching pain from shoulder to fingers—worst on inner side of forearm. Immediate and complete relief of pain. Lost sight of.

Case 24.—Female, aged 38, cook. History three years. Aching pain in shoulder and arm, also wasting. Immediate relief of pain. Remained well and at work nine months later. Lost sight of.

Case 27.—Male, aged 12, school. History four months; also wasting. Aching pain in ulnar border of forearm and hand. Immediate relief of pain. Remained well eighteen months later.

Case 30.—Female, aged 30, barmaid. History seven years. Pain in elbow and hand; also vasomotor symptoms and weakness. Immediate relief of pain

Six months later only occasional twinges. Six years later, "pain entirely gone."

Case 31.—Female, aged 15. History one month. Pain in shoulder and outer border of arm and forearm; also weakness. Immediate relief of pain. Remains well six years later.

Case 34.—Female, aged 42, secretary. History six weeks. Aching along ulnar border of arm; also wasting and vasomotor symptoms. Immediate relief of pain. Free from pain seven years later.

Case 37.—Female, aged 27, needlework. History two years. Aching pain in shoulder and arm; also vasomotor symptoms. Immediate relief of pain. Remains well seven years later. No change of occupation.

Case 38.—Female, aged 33, cook. History four years. Pain in shoulder and hand, also weakness; immediate relief of pain. Remains well three months later. Lost sight of.

Case 40.—Female, aged 42. History six years. Aching in shoulder and arm, also vasomotor symptoms and wasting; immediate relief. Still completely free from pain six years later. "Life worth living."

Case 42.—Male, aged 45, medical practitioner. History eight years. Very severe neuralgic pain in shoulder and arm generally, but chiefly along middle of forearm and outer border of hand. Immediate and complete relief of pain. Remains well and in full work eight years later. "Never any pain since I recovered from the anæsthetic. The operation altered my whole life."

Case 43.—Female, aged 34, housework. History one month. Pain in arm generally; also wasting. Immediate relief of pain. Seven years later, "operation completely successful."

Case 46.—Female, aged 53, housework. History seven months. Pain in right arm. Immediate relief of pain. Remains well eight years later.

Case 49.—Female, aged 18, cook. History two and a half years. Neuralgic pain in outer side of arm and hand. Immediate relief of pain. Remained well three months. Recurrence. Second operation for excision of scar tissue in track of previous subperiosteal resection. Complete relief, and remained well two years later. Subsequently lost sight of.

Relieved.

Case 12.—Female, aged 49, housework. History ten years. Aching pain in thumb; more recently pain in shoulder and arm, also wasting. Two months later pain gone. Eight years later reports herself much better.

Case 13.—Female, aged 38, letter-sorter. *Right side:* History fourteen years. Diffuse pain in arm, also weakness. Immediate relief of pain. Four months later free from pain. Three years later only has pain occasionally. Nine years after operation writes: "Pain nearly gone; I only get attacks. I am getting back all the power and strength again, and that after fourteen years of intense suffering and nearly lost the use of my arms and hands."

Left side: Condition similar. Nine months later still some pain. Eighteen months later has pain occasionally.

Case 15.—Male, aged 42, painter. History six years. Pain in neck, outer side of arm and back and outer side of forearm; also weakness. Immediate relief of pain. Two years later feels some pain after day's work. Subsequently lost sight of.

Case 22.—Female, aged 42, housework. History five years. Pain in elbow and fingers; also weakness. Complete relief of pain. Patient lost sight of.

Case 23.—Female, aged 24, school teacher. History six months. Pain in arms and neck, also wasting. Pain relieved at once. Eleven years later "sometimes a deal of pain at times."

Case 26.—Female, aged 50, housework. History 4 years. Diffuse pain in arm; also vasomotor symptoms and wasting. Eighteen months later very much better, but exertion brings on pain occasionally.

Case 35.—Female, aged 53, nurse. *Left side:* History two years. Pain in arm, chiefly outer border and flexor surface. Three years later much improved but gets pain after exertion. Ten years after operation "pain only after excessive work." *Right side:* Condition exactly similar.

Case 48.—Female, aged 19, clerk. History twelve months. Aching pain from elbow to wrist; also weakness. Immediate relief of pain. Eighteen months later, occasionally gets pain in cold weather. Subsequently lost sight of.

Vasomotor Symptoms.

In many cases the relief of the paræsthesiæ and other symptoms which I have grouped as "vasomotor" is immediate. Others however evidently require a considerable time, amounting to many months or even years, before recovery is complete or even approaches completeness. Thus Case 6 was noted, sixteen months after operation, as "remaining much the same as before," but seven years later the report is "no trouble of any kind for some years."

Result of Operation upon the Vasomotor Symptoms:
Namely—Objective (swelling, coldness, blueness).
Subjective (acroparæsthesia).

Cured.

Case 1.—Female, aged 13, school. History twelve months. Almost pure vasomotor case. In six months little result; in eighteen months cured. "No trouble of any kind."

Case 3.—Male, aged 27, stoker. History six months. Almost pure vasomotor case. Much immediate improvement—practically well in sixteen months. No change of occupation. Eight years later—"While in France

and under bad conditions I felt it several times but never bad enough to go sick with. Since my return I have not had the slightest trouble."

Case 4.—Female, aged 18, domestic servant. History three years. Also weakness, but symptoms chiefly vasomotor. Better immediately; still improving six months later; practically well in twelve months. No change of occupation.

Case 5.—Female, aged 51, housework. History three years. Also wasting. Better and still improving ten months later. Eight years after operation, no vasomotor symptoms.

Case 6.—Female, aged 50, housework. History eight months. Remains much as before sixteen months later. Eight years after operation, "no trouble of any kind for some years."

Case 10.—Female, aged 26, dressmaker. History eighteen months. Also wasting. Subjective sensory phenomena disappeared at once. No change of occupation. Ten years after operation, "no symptoms whatever."

Case 11.—Female, aged 52, housework. History three years. Almost pure vasomotor case. Relieved immediately; almost well in a month; after fourteen months had been perfectly well for some months; after three years remains perfectly well. No change of occupation. Ten years after operation, "just occasionally a little of the old feeling of numbness and pins and needles in the hand which occurs at night after doing more work than usual."

Case 14.—Female, aged 30, nurse. History five years. Also pain. Relieved immediately and still improving four months later. Eight years after operation, quite well.

Case 21.—Female, aged 25, no occupation. History two and a half years. Almost pure vasomotor case. Immediate relief. Patient lost sight of after two months.

Case 37.—Female, aged 27, fur sewer. History eight months. Also pain. Immediate disappearance of vasomotor phenomena; remains well eighteen months later. No change of occupation. Eight years after operation, "I have had no further trouble with my arm."

Case 38.—Female, aged 33, cook. History four years. Also wasting and weakness. Immediate relief of vasomotor symptoms. Three months later, "use of hand quite restored."

Case 39.—Female, aged 41, telegraphist. History two years. Almost pure vasomotor case. Some wasting. Immediate relief. Two months later, still improving. Fifteen months later, cured for some months and remains so.

Case 40.—Female aged 42. History six years. Also wasting. Vasomotor symptoms gone in a week. At work and remains cured six years later.

Case 42.—Male, aged 45, M.D. History eight years. Also pain and weakness. Immediate and complete relief of all symptoms. Remains well and in full work ten years later.

Relieved.

Case 18.—Female, aged 31, needlework. History eighteen months. Also pain and some wasting. Immediate relief. Two years later still improving, but symptoms recur in modified form after exertion. "Hand sometimes feels hot and tingling at night after exertion. Feels the cold greatly."

Case 25.—Female, aged 53, lady's maid. History ten years. Chiefly vasomotor case; but also weakness and wasting. Immediate relief; resumed work; very much better but not quite well three and a half years later. Ten years after operation, "left arm and hand painful when I have been doing too much. Otherwise I do not feel anything of it."

Case 26.—Female, aged 50, housework. History four years. Also, and chiefly, pain and weakness. Vasomotor symptoms improved at once; still improving after six months; in two years still better but not quite well. Heavy work brings on pain.

Case 30.—Female, aged 30, barmaid. History seven years. Chiefly vasomotor; also weakness and wasting. Improved at once; six months later better still and at work. Seven years after operation, "pain entirely gone, but in cold weather hand sometimes becomes useless."

Case 34.—Female, aged 42, secretary. History three months. Also pain and wasting. Vasomotor symptoms disappeared at once. Seven years later, "cold quickly stiffens the fingers."

Case 50.—Female, aged 49, housework. History twelve years. Chiefly vasomotor case at first; later wasting. Immediate relief of vasomotor symptoms. Patient lost sight of.

Unrelieved.

Case 19.—Female, aged 42, housework. History eighteen years. Also wasting. No improvement in six months. Lost sight of.

Case 41.—Female, aged 26, housework. History ten months. Only slight vasomotor symptoms; chiefly pain and wasting. No improvement in eight months. Lost sight of.

Muscular Wasting.

During the Discussion on Cervical Ribs at the Royal Society of Medicine in 1913, Thorburn stated that he had never been able to satisfy himself that atrophy of the hand muscles was ever entirely cured. This opinion was based upon an experience of twenty cases, observed over periods varying from twelve months to fourteen years. This was an important statement which, coming from such a source, could not be lightly passed over, and I have therefore reviewed my own cases with particular regard to this point. In thirty-one out of fifty cases wasting of the hand muscles was a pronounced feature. Twelve may be regarded as completely recovered both as regards bulk of

muscle and strength. In twelve cases the improvement was quite definite, but incomplete; whilst in only seven did any improvement at all fail to appear. It should be noted, however, that four of these seven patients were lost sight of before the result could fairly be judged. As might be expected, the recovery of the affected muscles takes a long time, and doubtless this is influenced by the treatment bestowed after operation. It is impossible to say what influence this factor may have had in my cases. As may be observed from the tabulated results it is on the whole the cases with the shortest histories which have done best as regards the muscular wasting.

RESULT OF OPERATION ON THE WASTING OF MUSCLES.

Cured.

Case 1.—Female, aged 13, school. History twelve months. General slight wasting. After six months no wasting to be detected. After eighteen months "no trouble of any kind; appears completely cured."

Case 6.—Female, aged 50, housework. History eight months. All intrinsics wasted. In sixteen months, little change; in eight years hand muscles quite filled out.

Case 8.—Female, aged 50, housework. History six months. Slight wasting of all intrinsics. After ten months, muscles filling out. After eight years muscles quite normal.

Case 10.—Female, aged 26, dressmaker. History two years. Marked wasting of thenar muscles. After two years muscles improving; in another six months quite filled out. After seven years remains completely well. No change of occupation.

Case 18.—Female, aged 31, housework. History eighteen months. Slight wasting of all intrinsics. After twelve months, "muscles increasing; hand stronger." After seven years remains much the same.

Case 23.—Female, aged 24, school teacher. History six months. Wasting of all intrinsics. After four years muscles much improved. After eleven years muscles full bulk and power.

Case 25.—Female, aged 53, lady's maid. History three months. Wasting chiefly of thenar muscles. After two years "muscles improving;" after three years "full bulk." After ten years remains well.

Case 27.—Male, aged 12, school. History three months. Marked wasting of all intrinsics. After eighteen months, full use of hand.

Case 33.—Female, aged 41, housework. History seven months. All intrinsics wasted. After twelve months marked improvement in bulk of muscle. After eighteen months "complete recovery." Seven years later "entirely recovered."

Case 38.—Female, aged 33, cook. History four years. Some wasting of all intrinsics. After two months visible improvement. After twelve months, complete recover

Case 39.—Female, aged 41, telegraphist. History two years. All intrinsics wasted. After three years, complete recovery.

Case 40.—Female, aged 42. History five months. Wasting: chiefly thenar. After eight months muscles much filled out. After five years, completely recovered.

Relieved.

Case 2.—Female, aged 38, housekeeper. History 5 years. All intrinsics, but specially opponens and abductor. After six months, no change. After seven years, "pain gone but fingers drawn."

Case 4.—Female, aged 18, domestic servant. History three years. Chiefly opponens and abductor. After twelve months, much improvement.

Case 7.—Female, aged 36, housework. History four months. All intrinsics but chiefly of thumb. After five months, much improved. Seven years later condition much the same.

Case 11.—Female, aged 49, housework. History twelve months. Wasting of abductor pollicis. After five years, "ever so much better." After ten years, remains practically well.

Case 20.—Female, aged 27, nurse. History fifteen months. Wasting of all intrinsics. After two years, muscles better; hand stronger. Not traced further.

Case 24.—Female, aged 38, cook. History three years. Wasting of all intrinsics. After nine months, very great improvement. Lost sight of.

Case 26.—Female, aged 50, housework. History four years. Wasting of all intrinsics. After eight months, muscles filling out. Not traced further.

Case 29.—Female, aged 18, housework. History two years. All intrinsics wasted, but chiefly thenar. After eighteen months, muscles fuller but still less than left. After nine years, no symptoms, but no further recovery in bulk of muscle.

Case 30.—Female, aged 30, clerical. History seven years. Wasting of all intrinsics. After six months, practically no change. Seven years later, "pain entirely gone. Strength of hand not completely restored."

Case 44.—Female, aged 52, needlework. History eighteen months. All intrinsics wasted. After three years, bulk of muscles much improved.

Case 47.—Male, aged 62, painter. History two years. After two years slight improvement in bulk of muscles.

Case 48.—Female, aged 19, domestic service. History twelve months, Wasting chiefly thenar. Eighteen months later, some improvement.

Unrelieved.

Case 5.—Female, aged 51, housework. History three years. Chiefly opponens and abductor. After nine months, stronger but muscles have not filled out. Seven years later, "condition much the same."

Case 17.—Female, aged 38, housework. History three years. Profound wasting of thenar eminence; slight of other intrinsics. After six months. "I fancy my hand is improved, but it is very slight." After seven years remains much the same.

Case 19.—Female, aged 43, housework. History five months. Wasting of thenar muscles. After six months, no improvement. Lost sight of.

Case 34.—Female, aged 42, secretary. History six weeks. All intrinsics wasted, but chiefly thenar. After seven years, no improvement but no worse.

Case 41.—Female, aged 26, housework. History ten months. All intrinsics wasted. After eight months, no improvement. Lost sight of.

Case 45.—Female, aged 53, married. History eight years. All intrinsics wasted. After two months, no change. Lost sight of.

Case 50.—Female, aged 49, housework. History twelve years. All intrinsics greatly wasted. In thenar muscles no response to faradism. Not traced.

Summary.

(1) Variations in the composition of the brachial plexus are apt to be associated with costal abnormalities, prefixation with a seventh cervical rib and postfixation with an abnormal first thoracic rib. There is, however, no regular relationship between the costal and neural anomalies.

(2) Of the several different types of cervical rib met with clinically, that which most frequently requires treatment by operation is represented by an abnormally large non-jointed costal process, continued onwards as a dense fibrous band, to be attached to the first thoracic rib behind the sulcus nervi brachialis (sulcus subclaviæ).

(3) Symptoms of gradual onset result from continual slight traumatism to the eighth cervical root or lowest cord of the plexus, caused by the tightening of the band during respiration and in certain movements of the arm.

(4) With a postfixed plexus symptoms referable to the first thoracic root may be caused by the pressure of a normal first thoracic rib.

(5) "Vascular symptoms" are vasomotor in origin and result from injury to the sympathetic fibres, shortly after their entrance into the eighth cervical and first thoracic roots.

The subclavian artery, whilst often occupying an abnormally high position in the neck, nevertheless rarely lies upon a bony cervical rib. It may be just held off from the first thoracic rib by the fibrous band.

(6) The results of operative treatment in fifty cases are given, the majority having been traced for a period of from two to twelve years.

Pain was cured in nineteen cases, and relieved in eight.

Muscular wasting was cured in twelve cases, relieved in twelve, and unrelieved in seven.

Vasomotor symptoms were cured in fourteen cases, relieved in six, and unrelieved in two.

EXPLANATION OF THE DIAGRAMS.

The diagrams have been constructed from rough sketches made at the time of operation. Those parts of the drawings which represent the abnormal ribs were made from the actual specimens removed, their relations to the other parts being shown in a diagrammatic manner. The dissections of a normal plexus (1) and of a plexus associated with a rudimentary thoracic rib (XVI) have been reduced to the same semi-diagrammatic form for the sake of comparison. The relative size of the nerve trunks as indicated in the diagrams must be taken as only approximately correct. A contribution from T1 is represented in all cases except those in which it seemed quite certainly absent.

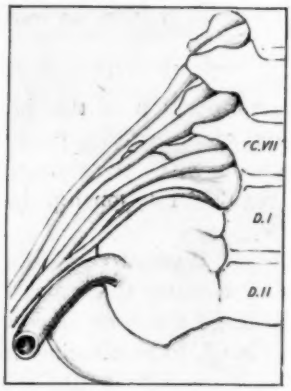


FIG. 4.—From a dissection of a normal plexus, showing the very small costal process of C7 vertebra, and the relation of the nerves with it and T1 rib.

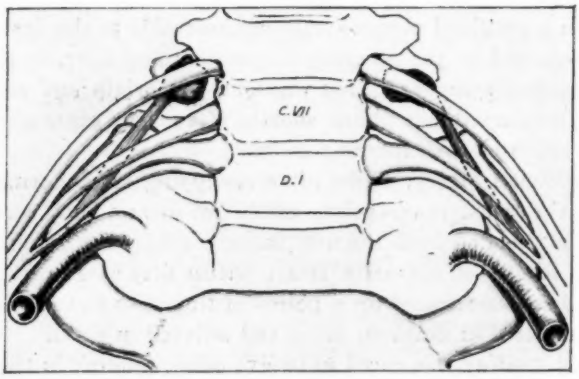


FIG. 5 is an example of Type 1, which radiographically was deemed to have no cervical rib. The report was "well marked transverse processes." This patient remains well eleven years after the bilateral operation.

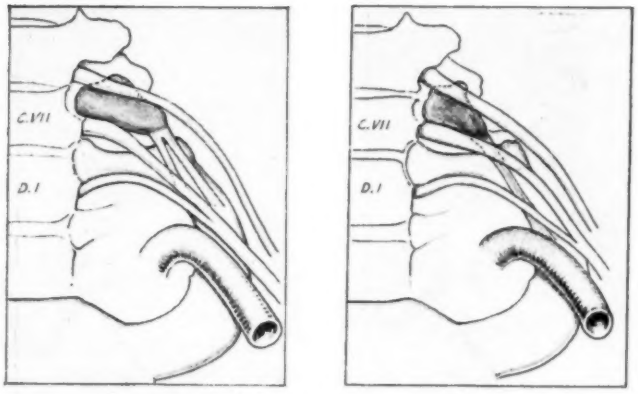
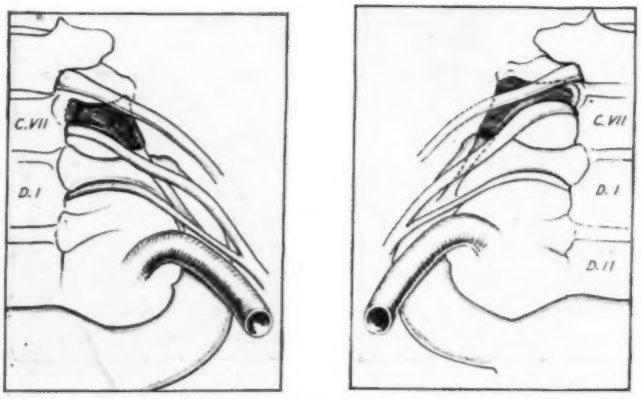
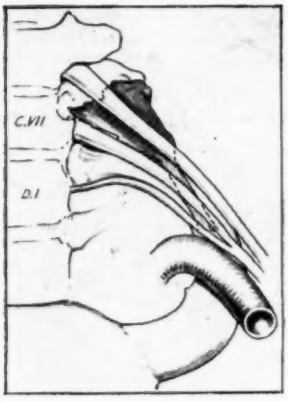


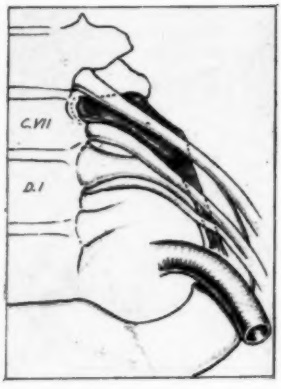
FIG. 6 represents a similar rib to those shown in fig. 3, but the rib is longer and was more pointed forwards, so that the band was more prominent. This patient remains well ten years after operation.

FIG. 7 is an example of Type 1, and may be taken as representing what in my experience is the commonest type which causes symptoms.

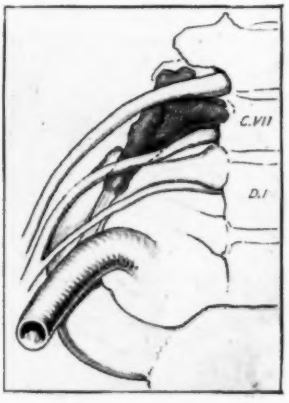


FIGS. 8 and 9 are examples of Type 2. The ribs are well formed at their proximal part, and the joints are perfect, but almost the whole body is represented by non-ossified tissue.





FIGS. 10 and 11 are examples of Type 2 merging into Type 3. The very sharp edged bone which separates C7 and C8 in fig. 10 is represented by a more rounded ridge in fig. 11.



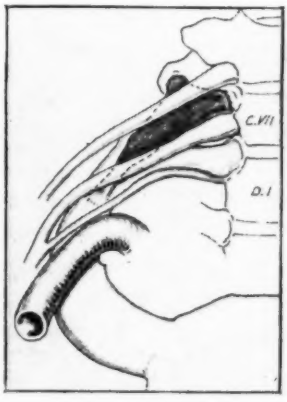


FIG. 12 is an example of Type 3, where the rib is long enough to carry C8 upon its bony portion.

FIG. 13 belongs to Type 3 and approximates to Type 4.

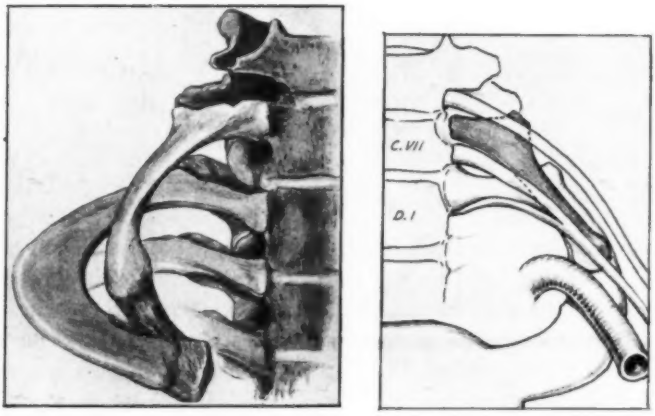


FIG. 14 from a specimen in the Museum of the Royal College of Surgeons (No. 505) showing a rib intermediate in character between Types 3 and 4.

FIG. 15 is an instance of Type 4, there being a joint between the enlarged end of the cervical rib and an irregular mass of bone on the upper surface of T1 rib.

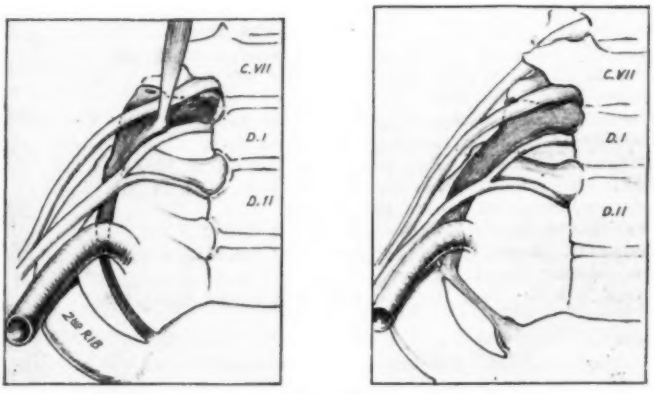


FIG. 16 is the only instance of Type 5 in my series.

FIG. 17 is constructed from a dissected post-mortem specimen shown to me by Prof. Wood Jones (10) and reported by him.

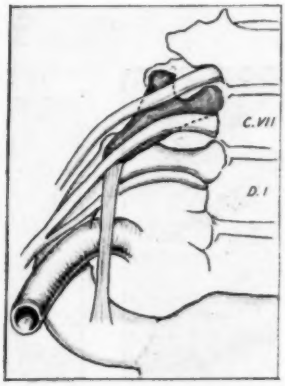


FIG. 18 represents a unique specimen which does not conform to any of the Types described. (See text.)

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ON STRUCTURAL LAWS IN THE NERVOUS SYSTEM: THE PRINCIPLES OF NEUROBIOTAXIS.[1]

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THE factors that determine the structures in the nervous system, the form of the neurones, their position and connections, have puzzled the minds of many neurologists.

This matter was first considered more thoroughly by embryologists, who, however, were chiefly interested in the problem of the connections between the central nervous system and the peripheral organs, the formation of nerve-roots.

One of those was Hensen, who assumed "that all nerves originated by an insufficient separation in the *primary* connections between ganglion cells and their peripheral organs during evolution." Hensen was thus a forerunner of the conception that a real separation of the cellular constituents of the body never occurs, but that its elements remain connected with each other. A similar conception of *syndesmism* was defended in England by Sedgwick, who stated that "Nerves are developments of the reticulum, elongated strands of the pale substance composing this reticulum, with some of their nuclei."

I shall come back later to this conception, which, although it may contain a true principle, can never explain the peculiar selectivity in the neuronal connections.

An opposite opinion was held by Balfour and His, who showed that the connections of the nerves with their end-organs were secondarily acquired.

Of these two leading embryologists, His was generally inclined to regard mechanical factors as the most important in the embryonic evolution, and he practically saw in the growth and arrangement of the nervous elements a purely mechanical problem.

He attempted to solve this problem by assuming that the direction of the nervous offshoots was determined by the places or paths of least resistance.

The Belgian histologist Dustin[2] has pointed out that by such *preformed forepaths* we are able to understand why the *regeneration* after cutting a peripheral nerve runs so smoothly, guided by the degenerated nerve-sheaths of the peripheral stump; whereas in the central nervous system, which does not exhibit any sheaths of Schwann, regenerating nerve-fibres rarely reach

[1] A lecture read in the University of London.

[2] Who termed this the hodogenetic principle.

their functional end-point, and thus the regeneration is mostly without result. Although this may be true, the presence of eventual forepaths is not sufficient to explain the *formation* of nerve-fibres and besides only displaces the solution of the problem.

If it be assumed that only a general tendency for making offshoots is present in the ganglion-cell, and that the *direction* in which the offshoots shall go only depends upon previously existing paths in the surrounding tissue, then this question remains, namely, by what influence is such a typical arrangement of the surrounding tissue established, so that just the *functionally correct* nervous connections result from it?

Especially the exquisite functional character of the connections in the central nervous system, where such conducting sheath-cells do not occur, remains entirely unexplained by this theory.

Another embryologist, Held, proceeds from the correct assumption, already formed by Hensen and Sedgwick, that the nerve-cells are *ab origine* connected by intracellular bridges, plasmodesms, previous to the formation of fibrils. Held was actually able to demonstrate that later on the fibrils (the nerve-tracts) grow into such plasmodesms. Held himself, however, is perfectly convinced of the fact that the general presence, the ubiquity, of these plasmodesms can never explain the selection in the formation of the fibrils. It can never explain why nerve fibrils grow in some plasmodesms and not in others.

He believes that the topography of the cells ([34], p. 47) and the direction of their axes ([34], p. 68) may act a part, but Held himself does not believe that these factors are sufficient to explain the typical *selection* in the formation of nervous tracts and says ([34], p. 270) that the determining principle has as yet escaped our scientific research.

A similar remark is made by Harrison, to whom we owe those valuable researches on the outgrowth of nerve-fibres in cultures, and who stated himself "that there is nothing in this work which throws any light upon the process by which the final connection of a nerve-fibre is established." That it must be a sort of specific reaction between each kind of nerve-fibre and its particular end-point is clear, according to Harrison.

The first who supposed a tropistic influence to act a part in these structures and who also accepted a reciprocal tropistic influence of the central nervous elements on each other was Cajal. The work accomplished by this author is extremely valuable.

Though—as is admitted by Cajal himself—it could not solve the problem, my respect for this excellent Spanish neurologist does not allow me to proceed without mentioning his theory.

Cajal believes that the connections of the nervous elements is determined by the secretion of *attracting and repulsing substances* and by the sensibility to these substances in the ganglion-cells.

Concerning the secretion of these chemotactic substances, which,

according to Cajal, may also be secreted by the ependyma cells,[1] this writer assumes that different parts of the central nervous system enter this stage of secretion at different periods of their embryonic development.

Cajal says that the stage of attraction *coincides with the evolution of the cell.* This, however, is apparently a displacement of the difficulty, for Cajal does not make any statement as to which factors determine the evolution of the cells and consequently of the secretion of those substances.

Thus he does not give an explanation concerning the cause of the local and temporary selectivity in this chemical process nor of the factors that determine the different nature of the axons and dendrites (the so-called *dynamic polarization of the neuron*).

Cajal himself remarks in his work on the retina: "Cette théorie présuppose des conditions préalables chimiques et morphologiques tout à fait inexplicables : on peut dire que cette théorie éloigne la difficulté sans cependant parvenir à la résoudre".[2] ([67], p. 240).

More important than Cajal's chemotactic theory is a remark by this author concerning the shifting of nerve-cells in the embryonic development of the nervous system, of greater importance even than he himself has realized.

This remark (not known to me when I commenced my researches on this question) is in perfect harmony with my own observations, and I am the more glad to be able to confirm Cajal's observations as to this point, since I arrived at a similar result in an entirely different way, namely, not by embryonic, but by comparative phylogenetic studies.

The remark then made by Cajal runs as follows: "If during embryonic development new axons pass to some region of the central nervous system, ganglion-cells may approach these axons in two different ways, either by sending forth long dendrites, or by a migration of the cell-body itself" ([69], p. 560).

Cajal mentions, as examples of a shifting of cells, the superficial layer of granular nerve-cells which in an early period of development

[1] Although I am not inclined to attribute an extensive part in this to the central spongioblasts it is a fact that different non-nervous elements (lemnoblasts, muscular cells, epithelium and even cicatrices of the connective tissue) are able in certain stages of their development to direct the offshoots of nervous elements.

[2] Child also ([17], p. 170) has recently criticized the chemotactic theory, and appears, like myself, to be an adherent of the bio-electric theory (see at the end of this paper).

cover the surface of the cerebellum and which later on shift into the depth of the cerebellum.

He also mentions the cells of the spinal ganglia which originally lie next to the neural tube, but later on shift a short distance peripherally away from the spinal cord.

Comparative researches on the oblongata and the mesencephalon have convinced me that this shifting of nerve-cells is a very common appearance, and that these shiftings of nerve-cells are determined by a process of *taxis* or *tropism* that is caused by the stimulation of such cells and their bio-electric consequences, which determine also the selectivity in the neuronal connections, and the difference between the dendrites and axons, the so-called *dynamic polarization of the neuron.*

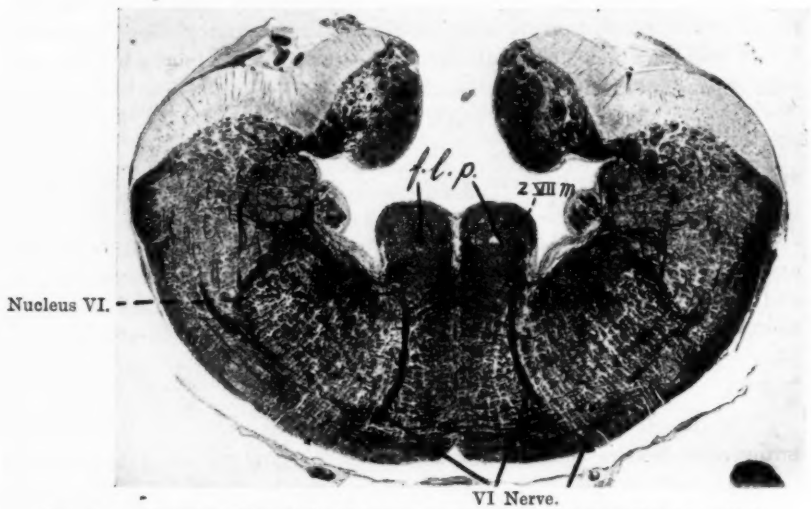

FIG. 1, A.—Dorsal position of the abducens nucleus in a shark (Acanthias) in which the dorsal longitudinal bundle is very large. After Van der Horst.

In what manner these processes can be engrammatically reproduced under embryologic conditions cannot for the present be stated. The same applies to the entire ontogeny however. Also the formation of the extremities for walking and grasping can only be explained by engrammatic factors, the character of which escapes us up to now. It may be that the electric potentials arising during evolution (Child) and whose sequence may be determined by engrammatic factors act a part in this process.

During the past twelve years I have registered the topographic differences of homologous cell-groups in the central nervous system of vertebrates where such differences appear most clearly in the nuclei of the motor roots of the oblongata (cf. Black and v. d. Horst), but also in many cells of the spinal cord, the mid- and forebrain (Herrick, Elliot Smith, Dart).

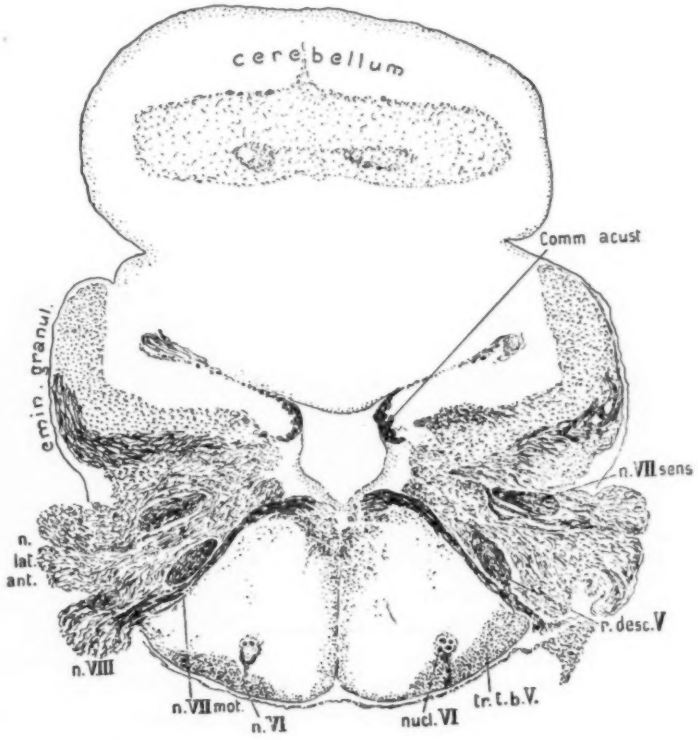

FIG. 1, B.—Ventral position of the VIth nucleus in a bony fish (Mugil chelo) with small dorsal longitudinal bundle and large ventral reflex tract (tr. t. b. V.). After Van der Horst.

As it is clear that the topography of these cell-groups is determined by the places from which the largest number of excitations reach the cells, we have plainly to do with an appearance of taxis or tropism, which I have termed *neurobiotaxis*, since it occurs in the nervous system during life.

For a better insight into this process of neurobiotaxis let us consider

figs. 1, A and 1, B, where the dorsal position of the abducens nucleus in a shark, with its large dorsal longitudinal bundle, strongly contrasts with the ventral position of the same nucleus in a bony fish where the dorsal longitudinal bundle is small, but where the ventral reflex-tracts, that influence this cell-group, develop to a much greater size (the tr. tecto-bulbaris ventralis : tr. t. b.).

In these cases it is evident that with an increase of stimulations in a certain tract not all the cells of the bulb approach this tract, but only certain cells, namely, such cells as bear a certain relation to this tract; whereas other cells, for instance, the cells of the facial nucleus that innervates the gills, do not migrate in the direction of this strengthened reflex field, since their function is not related to the function of these tracts.

So we see that there is a *selection* and that obviously a certain relationship is required for this process of shifting. We further see that this relationship is a functional one and that it consists in a simultaneous excitation of the enlarged stimulation centre and the motor-cells. If the motor-cells have a stimulative relationship with the enlarged centre, that is, if the motor-cells are in action at the same moment in which a nervous current passes through the enlarged tract, as is the case with the eye-muscle nuclei and optic reflex tracts, then the cells are attracted by those tracts, not otherwise.

This is anatomically expressed by the fact that the nucleus of the abducens shifts from one path of visual reflexes (the dorsal longitudinal bundle) to another region of visual reflexes (the tractus tecto-bulbaris ventralis). An increase of the central *taste fibres* of the oblongata however has not the slightest influence upon the position of the eye-muscle nuclei, but causes migrations of the nuclei of the jaws and gills.

It is thus seen that the relation of the (dendrites and) ganglion-cells in the nervous system is regulated in conformity with that law which in psychology has long been known as the *law of association*, in which law (in all forms in which it may appear) the simultaneity or direct successivity of the excitation is the chief point.

This observation, made with motor-cells and their dendrites, led me to study more fully the course of the axons, and I found that a critical observation of the relations existing between the regions where they begin and end show the same law, namely, that only a functional relationship between two regions can cause an axonal connection between those regions. As a simple example it may be mentioned that axonic connections may arise and do in fact arise between the visual centres of the brain

and the vestibular centres on account of the fact that visual impressions and vestibular impressions very often reach the brain simultaneously.

Thus, *associated stimulation* was found to be the determining factor in the neurotropic appearances, and I was able to formulate the facts in the following words :—

(1) *If several stimulative charges occur in the nervous system, the outgrowing of the chief dendrites and eventually the shifting of cells takes place in that direction whence the largest number of stimulations goes to the cell.*

(2) *This outgrowing or shifting, however, only takes place between stimulatively correlated centres ; temporarily correlated excitation acts a part also in the connections of the axons.*

FIG. 2 shows that the outgrowth of the dendrites and the final shifting of the cell body itself takes place in a stimulo-petal direction, whereas the course of the axis-cylinder is stimulo-concurrent.

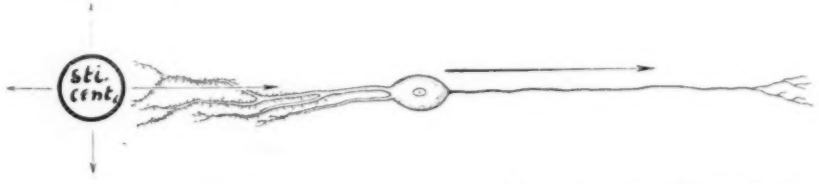

FIG. 2, A.—Giant dendrites grow out in the direction of the centre from which the stimuli proceed (sti. cent.).

FIG. 2, B.—The cell body itself (perikaryon) has shifted in the direction of the stimulation centre. The dendrites have shortened, the axis-cylinder has correspondingly enlarged.

Comparative anatomy of the fibre-tracts in the central nervous system gives plenty of evidence that this is always a leading principle in the formation of tracts. Now, however, the question arises: if associated excitation causes the formation of dendrites and the shifting of ganglion-cells as well as the formation of axons, how may we then explain the different character of the dendrites and the axon, the so-called *dynamic polarization* of the neuron?

Whereas the approaching of the dendrites and nerve-cells towards

the centre of excitation is a stimulo-petal tropism, that is, a tropism that runs to the centre of stimulation, the problem with the axon is much more difficult since the axon apparently does not grow out towards the excitation centre, but in the same direction as the nervous current that irradiates from this centre, and consequently grows away from the excitation centre (fig. 2).

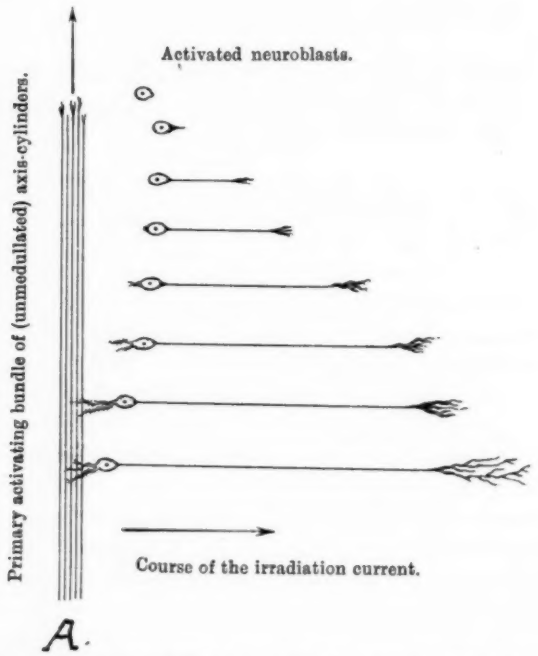

FIG. 3.—The activation of adjacent neuroblasts by a non-myelinated growing bundle of nerve-fibres. The vertical arrow indicates the direction of the growth and the stimulation current in the primary activating bundle which has started at A. The horizontal arrow indicates the direction of the irradiating influence, perpendicular to the primary bundle. The proximal cells are sooner and consequently further differentiated than the distal cells. After Bok (slightly modified).

That the axon actually does grow out in the same direction as the excitation current, and that this current plays an important part at its formation, has been proved by my former scholar, Bok (1915).

Bok found that when a bundle of unmedullated nerve-fibres grows out and passes neuroblasts on its way, these neuroblasts become activated by that bundle and send forth an axon in a direction perpendicular to

the activating bundle, apparently growing in the same direction as is taken by the current that irradiates sideways from the growing bundle (see fig. 3).

This fact was established in a manner that does not admit of any doubt, since it was found that the neuroblasts lying in the region of the growing bundle were only activated if the activating bundle reached their level, apparently by stimuli irradiating therefrom.

Thus here, too, we find a process that, like the outgrowth of the dendrites and the shifting of the cells, is determined by a nervous current.

At the same time, however, we perceive that the axon (in contrast to the dendrites and the shifting of the cell body) grows away from the region of stimulation.

Whereas the growth of the dendrites is a stimulo-petal tropism, the growth of the axon bears a *stimulo-fugal*, or better, a *stimulo-concurrent character*.

Here I may call attention to the fact that both the neuroblasts and placode cells, as long as they have not developed dendrites, may shift with the nervous current, away from the excitation centre, contrary to that which occurs later with the ripe ganglion-cells.

It is clear, however, that the *functional connection* of the outgrowing axon cannot be determined by this process of irradiation alone, as was realized by Bok, who came to the conclusion that its final connection, its end-point, is determined by the chief law of neuro-biotaxis, namely, by a stimulative relationship between the place where the axon starts and the region in which it will end.

I shall return to this question of *selectivity* in the axonal endings at the end of my lecture. The stimulo-concurrent character of the axon and the stimulo-petal character of the dendrites and ripe ganglion-cells once being established, it puzzled me to find out the physico-chemical causes of these facts.

In the first place it may be asked how it is possible that in one and the same cell two opposed tropisms, a stimulo-petal tropism of the dendrites and a stimulo-fugal tropism of the axon, can occur?

Considering this question I felt inclined to believe that bio-electric influences, a species of galvano-tropism, exercised a leading influence here.

I thought so, *firstly* on account of the electric phenomena well known in nerve physiology, *secondly* on account of the opposite polarized character of dendrites and axons, and at last on account of

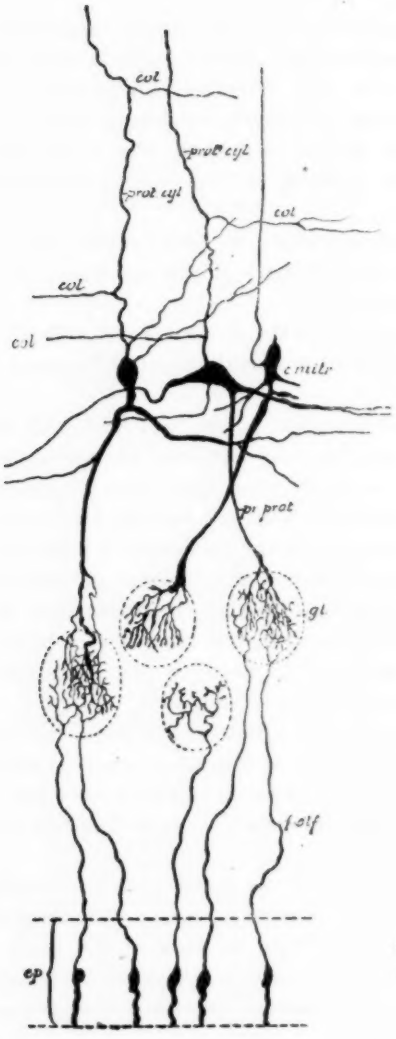

FIG. 4.—After Van Gehuchten. Notice the perpendicular course of the collaterals (col.) on the axis cylinders (prot. cyl.) of the mitral cells.

the fact that collaterals of axons very often run (at the beginning) exactly perpendicular to the mother axon, as for instance is seen in the drawings given by our too early deceased colleague, Van Gehuchten. Fig. 4 shows that collaterals grow perpendicularly from the axon, just as the axons of the young neuroblasts run perpendicular to the activating bundle.

A similar process, reminding us forcibly of bio-electric fields, is demonstrated by the perpendicular position of the dendrites of the Purkinje cells on the parallel fibres in the cerebellum (see fig. 5).

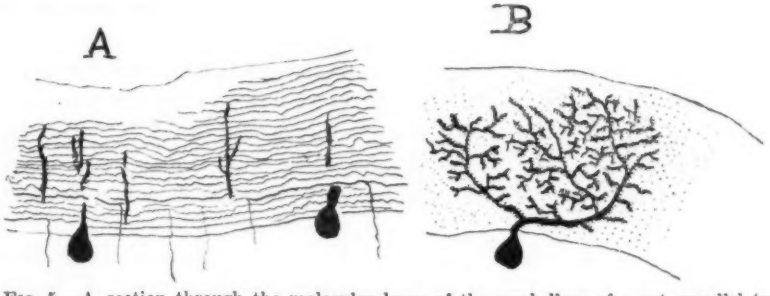

FIG. 5.—A, section through the molecular layer of the cerebellum of a cat, parallel to the parallel fibres of the layer. B, section perpendicular on the parallel fibres showing the spread of the dendrites of the Purkinje cells in one plane, perpendicular to the parallel fibres.

Analogous relations are found in the spinal cord of the lamprey where the dendrites of the motor cells stand perpendicular on the unmedullated longitudinal tracts (Tretjakoff).

The fact that many of these dendrites reach the periphery of the cord, where they may end in thickenings, has suggested to Tretjakoff the idea that their arrangement is due to assimilatory influences, since the spinal cord of the lamprey does not contain blood-vessels and the assimilatory substances come from the perimedullary vessels. Although I do not doubt that their close relation to the margin of the cord may have to be explained in this way, it does not seem probable to me that the *perpendicular position on the axis* of the cord must be attributed to this alone, since the contact with the periphery might also be obtained if the dendrites spread in different levels, most easily even in a fan-like way to the dorsal and ventral surface in a level parallel to the longitudinal axis of the cord, since the postero-ventral dimension of the cord is only very small in this animal. Besides the spreading of dendrites perpendicular to unmedullated fibres occurs also in the molecular layer of the cerebellum (*vide supra*), where such a spreading is not influenced by peripheral blood-supply since the molecular layer itself already contains a number of capillaries before the typical arrangement of the dendrites of Purkinje cells arises, which only takes place after birth (Addison).

It thus seemed to me that the neuro-biotactic process is based on bio-electric principles and that we have to do here with a sort of galvanotropic process (1908 and 1917).

Now by galvanotaxis or galvanotropism we understand the phenomenon that a living being, or part of it, when influenced by a constant electric current of a very low potential, has the inclination to turn to a certain pole, in most cases to the negative pole (the cathode).

Thus the roots of plants grow towards the negative pole, unicellular animals shift in the same direction, and the tentacles of a medusa move towards the negative pole (towards the cathode).

The interesting point, however, is that *this process is reversible.*

If the object, as for instance the roots of growing plants or unicellular animals, be brought into a stronger solution of potassium salts the tropism will be reversed and the object may turn towards the positive pole (the anode), instead of to the negative one.

This has probably to be explained by the influence of the electrolytes in the solution on the electrolytes in the vegetable skin, the presence of which also accounts for the blaze-currents, described by A. D. Waller.

The reversal of the tropistic process, then, must probably be explained by surface condensations of electrolytes, such as colloidal-chemistry shows us.

For we know from Hardy and others that albumin-like materials also show a shifting in a galvanic current, the process of *cataphoresis*, and it is very interesting that this cataphoresis may also be demonstrated experimentally with the nerve constituents, as has been shown first by Hermann and confirmed by Ingvar and myself. This shifting of colloidal materials can be reversed by acids, and directed towards the negative pole (cathode). Now there is a good deal in these reversible processes that seems to be applicable to the nervous system in connection with the physiology of excitation and conductivity.

In the first place, we know that a part of the surface of a nervous leader, in excitation, forms a cathode with regard to its surroundings which so to say represent an *anodic field* with regard to the surface of the excited centre.[1] (Fig. 6.)

The importance of this fact for the formations in the nervous system has been confirmed by Child, who also proves to be an adherent of the theory of bio-electric potentials as leading factors in the formation of the neuron (see p. 145 of this paper).

The nerve cells, that are now situated in the surroundings of that electro-negative excitation centre, first produce (probably on account of a change in surface tension, as is also supposed by Marinesco) a positive offshoot, corresponding to the irradiation of the nervous current from the excitation centre. This first kationic offshoot is the axon.

[1] Which inside is also positive.

This growing away from the excitation centre may be followed by a shifting of the cell itself in the same direction, so long as no dendrites occur, as for instance is seen with very young neuroblasts and placode cells.

Child has recently confirmed this point in my conclusions, emphasizing that ([17], p. 187) the region of origin of the axon is electrically determined in each cell by the electric currents of its environment.

It seems probable to me, that positive ions such as potassium act an important part in the axonal growth just as different concentrations of electrolytes act an important part in the nervous current itself, as has been demonstrated by Macdonald.

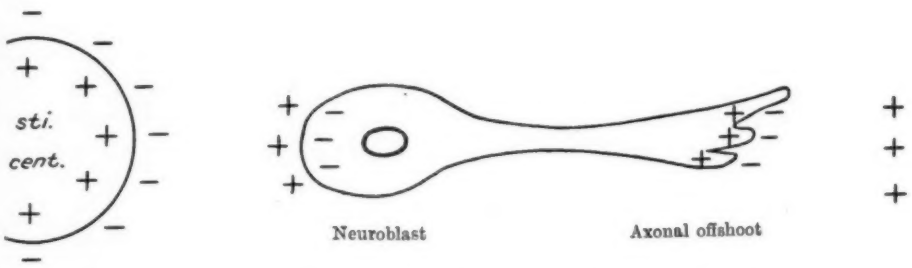

FIG. 6.—Eventual division of electrolytic potentials in the neuroblast (right) during the outgrowth of the axon by an action current.

We know that the axon more than other parts of the neuron contains large quantities of potassium compounds, as was pointed out by Macdonald, Macallum and Menten, independently of each other and in different ways. This high percentage of potassium must favour the stimulo-concurrent character of the nerve fibrillæ lying in it, that is the stimulo-concurrent growth of the axon. Consequently, just as Waller in his "Signs of Life" (p. 148) is inclined to consider the action current of the nerve as affected by kationic transport from the seat of action, so I consider even the outgrowth of that axon as being greatly influenced by such a kationic transport. *The outgrowth of the axon apparently is influenced by the action current*, which may also explain the influence of slight stimulations on regeneration.

And this is not so strange after all, since we know that the function of an organ and the growth of an organ are only two different aspects of the same thing.

Although I could not expect that this conception of the electric

character of the formation of the axon—which was a mere hypothesis until some months ago—should so soon be confirmed experimentally, I am in the happy position now of being able to state that the electric galvanotropic character of the outgrowth of the axon has been confirmed experimentally in embryonic tissue in serum cultures, in Harrison's laboratory, by our Swedish colleague, Sven Ingvar [44], who found that such an outgrowth may be determined by a constant galvanic current of a strength of 2 to 4 billionths of an ampère, density approximately $\frac{1}{1000}$ to $\frac{1}{2000}$ δ, non-polarizable electrodes.

So much as to the formation of the axon. At a much later stage the *dendrites* arise, and somewhat later still the cell body itself may commence to shift in an *opposite* direction to the axon, namely, towards the centre of excitation (thus stimulo-petal).

The stimulo-petal, cathodic tropism of the dendrites and of the perinuclear cell-plasm coincides with the appearance of the substances known as Nissl-bodies, which contain oxydases and catalases, and consequently only takes place when the neuron is in a far more advanced condition of development.

This tropism of the dendrites and the cell itself is in perfect harmony with the phenomena of excitation and contraction at the cathode according to Pflüger's law, as evinced in any protoplasm which, for instance, has been found for amœba by Loeb and Maxwell, and causes these parts to go to the field of excitation.

That the galvano-tropism of the dendrites is actually opposite to the galvano-tropism of the axon has also been confirmed experimentally by Ingvar in his serum cultures of the chick embryo.

If we consider the outgrowth of dendrites and the shifting of the ripe cell body as a tropism in the direction of the negative excitation surface, we must see whether there is any influence in the cell or dendrites that may make their tropism opposite to that of the axon in a galvanic field.

Now in trying to explain this opposite tropism of the dendrites (and of the ripe ganglion-cell), we are immediately struck by the fact that this cathodic shifting only occurs with those parts of the neurone which contain Nissl substance.

The axon, which contains no Nissl substance, exhibits a shifting in the opposite direction. That, indeed, this Nissl substance may have something to do with the cathodictropism of the dendrites and ripe cells, is further made probable by the fact that as long as the young

neuroblast contains no Nissl substance[1] it does not show the cathodic tropism, but even the opposite of it, and that the cathodic tropism occurs only when chromidial substance is developed in the cell which runs nearly parallel with the formation of the dendrites. It fails also to occur with placode cells, which contain no chromidial substance.

What then may be the influence of the chromidial substance on this process?

Now it seems that Hardy's work on cataphoresis, which, according to Greeley, may be applied to intra-protoplasmatic colloidal suspensions, furnishes us with the solution of this problem. We know that the Nissl substance during life (Cowdry), particularly during the development of the cells (van Biervliet), is in a more or less fluid condition, and that it surrounds the fibrillar substance.

This chromidial substance is a very complicated one, as has been demonstrated by Holmgren and Marinesco, of whom the latter working in Mott's laboratory showed the presence of *oxydases* in it. Thus much, however, is certain, that it is an acid derivative (a compound of nuclein acids with iron), and its acid character is also demonstrated by the fact that it can be coloured only by a basic strain.

According to Hardy's researches however, acids favour the shifting towards the cathode of the colloidal fibrillæ that are suspended in it.

Also the liberation and accumulation of the Nissl substance at the pole of the neurone that is opposite to the potassium accumulation agrees with electrolysis.

The late appearance of this chromidial substance in the cell-body, in which it appears only when the axon has already extended its growth over a considerable distance, would also make us understand the late formation of the dendrites. It thus seems that the developmental character of the whole neurone may be explained by bio-electric forces, and is in perfect harmony with the bio-electric phenomena known in nerve physiology: the growth of the axon depending on the action current, whereas the formation and contraction of dendrites is homologous to the cathodic outgrowth and contraction of pseudopodia, in a galvanic current and is favoured by metabolic processes, related to stimulation.[2]

[1] Whether the granulations which G. Levi saw ([46], p. 169) in his migrating cells, when they shift are to be compared with chromidial substance I do not know. I hope this excellent Italian histologist will continue his experiments which seem to me of utmost importance.

[2] That the stimulo-petal shifting of the dendrites and ripe cell-body is favoured by special chemical activities occurring in the dendrites and perikaryon is made probable by the fact

Mono-axonism and Polydendritism.

There are more characteristics of the nerve-cell that may be considered and explained from this standpoint. The *first* is that only one axon leaves the cell,[1] whereas a large number of dendrites may grow out from the cell-body in any direction towards several centres of stimulation (*mono-axonism and polydendritism*).

To explain the *mono-axonism* we must first realize that, with a polar tropism, as the galvano-tropism pre-eminently is, an object under the influence of a bio-electric current places itself so that the influence is equally great on both sides of the object. Then only does a condition of equilibrium occur. Thus the perpendicularly, stimulo-concurrent outgrowing axons of neuroblasts (fig. 3), as well as the perpendicular position of the collaterals upon the axis-cylinder (fig. 4), are natural consequences of the perfectly polar irradiation current. If now two (or more) different excitation centres simultaneously activate one cell, we may expect to meet with only one axis cylinder in the resultant line of both (or more) current directions (in the resultant of the bio-electric field), since it is only in this line that an equal influence on both sides of the growing axon is realized.

But what will happen, if two or more activating centres exercise their influence, *not simultaneously, but after each other upon the same cell-body?*

One of these activating centres will be necessarily the first and causes the formation of the axon hillock.

When, however, an axon hillock has commenced to grow, *i.e.*, when an efferent zone of fibrils has been formed in the cell-body, we may expect that the opportunity, offered by this zone, on account of

that their constituents act a much greater part in the assimilation of oxygen (on account of the oxydases and catalases occurring in the Nissl substances) and not in the axon.

Stimulation and oxygenation probably run parallel here (stimulation setting free the catalases) and sustain not only each other (Lillie) but also the neurobiotactic process as is suggested to me by Sir Fred. Mott. The influence of metabolism on the growth of dendrites cannot be denied and is proved by the Cajal cells and the perimedullary dendrites in the lamprey (see above) which has no intraspinal blood-vessels and where the dendrites spread very richly on the periphery of the cord where they end in thickenings, just as ependymal and glia cells do, as if to have more ample contact with assimilatory substances. Since stimulation and assimilation run frequently parallel this may also act a part in the direction of the dendrites to the source of stimuli. That metabolic processes may influence the galvano-tropism has also been stated in lower organisms, since Terry found that "the galvano-tropism of volvox depends upon its state of chlorophyll metabolism" ([77], p. 243).

[1] The horizontal cells of Cajal may exhibit two or more axis cylinders. These do not proceed however from the cell-body, but originate at great distances from each other, from different dendrites.

its greater conductivity, is so favourable, that every new current that runs over the cell, instead of forming a new axon in another place of this cell, will make use of the opportunity of better conductivity, already present, the more so since on account of the originally irradiating character of nervous currents, these currents, if they reach the cell, will necessarily always cover the whole of it, and thus necessarily meet the axon hillock. The first formed zone of efferent fibrils, the axon-hillock,[1] becomes thereby the favourite conveying path for all the stimuli that run over or through the cell-body.

The relations for the formation of dendrites are, however, altogether different.

When a stimulus appears in the vicinity of the cell, the most adjacent part of the protoplasm of such a cell may shift in the direction of that stimulus. With the equality of that protoplasma and the ubiquity of the Nissl substance in the whole cell (with the exception of the axon hillock) this process is, of course, not restricted to one field, and finds no place of predilection, except the one that is nearest by. Centres of excitation situated elsewhere may, and even must, cause new protoplasmatic outgrowth in their own direction, if the dendrites that have previously grown out are not on their way.

So we find that mono-axonism is a result of the polar localization of the anodotropic part of the cell, whereas polydendritism is based on the fact that the cell-plasm has no place of predilection and is everywhere sensitive to the cathodic tropism.

The Selectivity in the Formation of Neuronal Connections.

I have already said that the anatomical relations as found in the nervous system and the processes of cell shifting clearly point to the fact that the relationship which determines the connections is the synchronic or immediate successive function of the elements.

This fundamental law of neurobiotaxis does not merely show us that the well-known law of association in psychology is also a neurobiotactic law, but it also shows how wonderfully polar the whole character of the tract formation is, and how well it fits in with the class of bio-electric phenomena. For the purpose of explaining this selectivity I must draw attention to the following points.

[1] The polar character of which has been demonstrated by Held to coincide with the diplosome-centre.

We may assume that a state of excitation, once started in a budding axon, proceeds rapidly and a strong current of internally positive potential reaches the buddingcone of the axon. That this is more than a mere supposition follows from the researches of Scaffidi[1] (and Viale) who proved that, if a nerve after section starts to regenerate its budding cone shows a positive potential current, that reminds us of an action current and may be called regeneration current or—as I do in embryonic tissue—a *growth current*.

If we now assume that in the neighbourhood of this budding cone several nerve-cells are situated, one of which is already in a state of electric dissociation, while the others are not, it will be evident that the cell which is in a state of ionization is the only one that presents a selective point to the budding axon.

The potential, that continues along the budding axon, may find its natural counterpart only in the already ionized cell, and not in cells which are not stimulated and which are consequently indifferent objects, not presenting any predilection.

The principal part in establishing the connections between the growing axon and the cell or dendrites with which it is going to be connected may be played by the raised *positive surface potential* which appears near the cell shortly after some previous stimulation and which immediately follows its stimulation (see fig. 6). Or, in other words, the growth-current of the budding axon will find a place of predilection in a neurone that has been in action shortly before, just as with ships in a battle line one ship sails in the wake of the ship that precedes.

In the physiology of nervous currents there are several facts which are in favour of the supposition that an immediately prior excitation exercises a directing influence upon the course of new excitations occurring in the nervous system, since Sherrington emphasizes, "that the threshold of a reflex is lowered by the excitation just preceding its own," and this also explains why a connection just established between two neurones (a synapse) "is an apparatus for co-ordination and introduces *a common path*," i.e., of several other excitations ([75], pp. 184, 351).

This principle of selectivity based on the influence of a just preceding state of function as forming a centre of attraction for other

[1] *Zeitsch. f. allg. Physiologie*, 1910, Bd. xi, S. 345: "Die Schnittflächen der Nerven, welche nach der Durchtrennung *in situ* bleiben, sowohl nach wenigen Minuten als nach verschiedenen Monaten fast immer positiv u.s.w. Die positive Ladung der Schnittflächen verschwindet rascher nach der einfachen Durchtrennung, d. h. wann Verschmelzung folgt."

nervous currents or budding axones, becomes of use in a most interesting way, in making us understand the connections of the nervous system with the muscles. Bok (1917) has shown that the connection between certain muscles with sometimes widely distant places of the central nervous system, has to be explained by the fact that a contraction of a muscle (the formation of which precedes the formation of nerve roots) acts tropistically upon the central nerve fibres.

A contraction, or an analogous condition, raised by some external non-nervous circumstance, attracts action currents which happen to be present at that moment in the longitudinal tracts of the central nervous system, thus leading at the same time their growth.

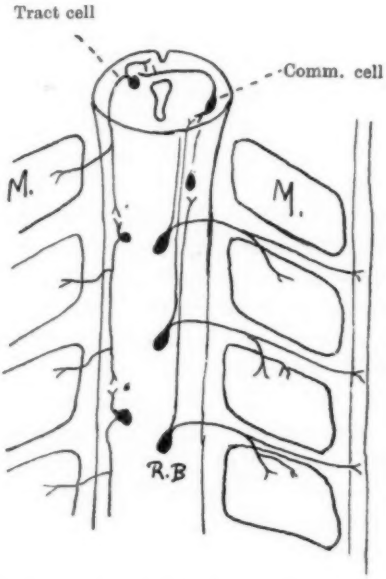

FIG. 7.—Relation of the spinal cord to the myotomes (M.) and skin. On the right hand, R.B., Rohon-Beard's sensory cells for skin and muscle sensibility. To the left are collaterals forming motor nerve-roots. (After Herrick and Coghill.)

In accordance with this conception is the fact that the first motor roots as they occur in invertebrates and as Coghill found them in larvæ of amphibia, originate as collaterals of longitudinal tracts (fig. 7).

Only later the neuroblasts lying next to such longitudinal tracts are activated to form axons, that replace these collaterals and form the

real motor roots. Hence it follows that originally the myotomes attract the action currents present in the central nervous system immediately after the moment of their contraction, or, in other words, *that the process of contraction is originally only integrated, not caused by those central currents.*

Later on, when the connection of the roots with the myotome has been established, the contraction may of course be caused by those central reflexes. Now I said that cat-ions as potassium probably exercise a considerable influence in the growth of the axon just as according to Macdonald and Waller it does in the action current of the nerve. Similarly we find that potassium may act a part in the process of the entering of nerve-fibres into the muscle, since Boeke found the nerve-fibrils to end in the anisotropic layer of the muscle in which, according to Macallum's reactions, potassium is localized (see also Woerdeman). I hardly need to say that in this respect also the researches of Howell, and specially those of Zwaardemaker, concerning the rôle of potassium in the transmission of stimulation are of utmost importance.

It is probable that in embryonic objects the proliferation of muscle tissue has the same influence as the function of adult tissue and that proliferating muscle-tissue thus may attract irradiations of the nervous currents from the spinal cord, in the same way as the proliferating connective tissue attracted the collaterals of the roots and even of the lateral funiculi in the experiments of Cajal.

Child recently has called our attention to the probability that during the evolution of tissue electric conditions occur very similar to those occurring in stimulation.

The sequence however in which this embryonic proliferation takes place must be caused by engrammatic conditions the character of which as yet entirely escapes our conception.

It is evident that there are many more questions in nerve histology and nerve physiology that may be considered from this standpoint, which, I hope, may be useful in giving the missing link between the structural and functional features of the nervous system.

I am afraid, however, that I have taken already too much of your attention and I will finish here by stating—what perhaps you have already stated yourself, when listening to me—that a large part of th researches forming the stones that enabled me to build this theory are given by others, and not least by your own countrymen.

POSTSCRIPT.

It was only after delivering this lecture that I came to study Child's valuable book, "Origin and Development of the Nervous System, from a physiological viewpoint," a very interesting contribution to our knowledge of development of pattern.

I have not been able to discuss its contents fully in this paper, though I have added some references to it. I will not omit recommending it to those who are interested in the directing influence of electric potentials, and I am glad that Child and I fully agree in the importance of these potentials.

Reserving a fuller discussion for a later paper, I will only add that I do not agree with him in ascribing the development of ventral roots and dorsal roots to two principally different types of polarization—his first and second type.[1] Neither do I agree with his supposition "that it is not necessary to assume that the dendrites react differently to the electric current than the axon." ([17], p. 195.)

Apart from my own deductions on this point I may refer to Ingvar's statement that the offshoots that grow to the cathode and those which grow to the anode in his experiments show a difference of character ([44], p. 198), and further to a personal communication of this author to me that it seemed to him that one of these offshoots was the axon, and the opposite one a dendrite.

I further must state that the division of electrolytes which Child gives in his fig. 57, as presenting my idea about this matter, does not represent my idea.

I have in the paper quoted by Child purposely not given a schematic indication of the division of electrolytes in the cell, because I could not do so, and certainly would not like to express it in such a simple scheme. I would rather give it (but still with great hesitation) as it is given in fig. 6 of this paper, for the development of the axon.

It seems to me that the last-mentioned scheme agrees with the accumulation of the more or less acid chromidial substance inside the pole of the neurone opposite to the axon-formation, where later the dendrites occur, and where oxidation, and also acid constituents (that is, negative potentials) are really found later on, as is to be expected from what we know of electrolytic dissociations. I am afraid, however,

[1] Such different types, apart from the artificial assumption of their existence in the nervous system, are, even if they were possible, doubtful, as long as the question of plasmodesmic pre-formed paths (that is of tissue continuity) is not sufficiently settled. (Compare Paton and Neal.)

that at present we are not yet able to state with any amount of certainty the exact division of potentials in the tissue even in serum culture experiments, since the applied potentials may be reversed by membranes or Helmholtz-Quincke layers, to which Child also calls attention.

The chief point is that we agree that electric potentials are the moving factors. As far as concerns their details the neurobiotactic phenomena will offer still many difficulties and controversies, the whole problem being a very difficult one.

A point in which we are especially grateful to Child is his pointing out in connection with Lillie's work the relation between oxidative processes and growth in certain directions (gradients). Specially the relations of the dendrites as found in Petromyzon (Ammocœtes) comes thereby nearer to our conception. (See p. 135 and footnote [2] on pp. 139 and 140.

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A CLINICAL AND EXPERIMENTAL CONTRIBUTION TO THE PATHOGENESIS OF DISSEMINATED SCLEROSIS.

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THE investigations with which this paper deals were begun in the autumn of 1913, and resumed in 1920 after an interruption of five years caused by the War. At the time when our work was begun no evidence from the experimental side had been published which served to throw any light on the obscurity in which the pathogenesis of disseminated sclerosis has so long been shrouded. In October, 1913, a paper appeared by Bullock [2], who claimed to have transmitted the disease from man to rabbits, while in 1914 an exhaustive work was published by Siemerling and Raecke dealing with the morbid anatomy and histology of the disease. During and since the War other evidence was forthcoming in the direction of a solution of the problem confronting us, and it is mainly on this account that we have decided to publish the results of our investigations. It can at once be stated that our experimental results are almost entirely negative, and we are well aware that their publication may appear to some unnecessary. We feel, however, that negative evidence cannot be entirely disregarded, especially in view of the fact that much of the positive evidence which has recently appeared is to our mind unsatisfactory and unconvincing.

The clinical material on which this work was carried out was obtained from the wards either of the National Hospital, Queen Square, or of St. Thomas's Hospital. To the members of the staffs of both hospitals who gave us every facility for our investigations we wish to tender our grateful thanks.

Thirty-five cases have been investigated clinically and bacteriologically, while animal inoculations have been carried out in fifteen instances, in two cases with material obtained post mortem.

Clinical Study.

Although it is not our intention to enter into a detailed discussion regarding the differential diagnosis of disseminated sclerosis, nevertheless this aspect of the matter must not lightly be passed over. In more than one recent publication, for example, dealing with the transmissibility of the disease to animals, too little importance has been attached in our opinion to the clinical side. We are merely told that the case providing the material to be injected was one of "typical multiple sclerosis"; or else a brief clinical résumé is appended from which it is not always clear that the patient actually had this disease. In three cases investigated by us the provisional diagnosis of disseminated sclerosis was proved to be incorrect, and in two others (Cases IV and XIII) it remained doubtful. (*Vide* Appendix.) Of the three patients wrongly diagnosed, none of whom are included in our series, one proved to be a case of syringomyelia, while the other two were cases of cerebrospinal syphilis.

In no disease is accurate history-taking more important than in the one under consideration, and in a large majority of cases a diagnosis can be made from the history alone. The patient's description of the onset and character of the various symptoms is usually sufficient to make it clear that widely separated areas of the central nervous system have been affected at the same or at different times. This feature differentiates disseminated sclerosis from all other common diseases of the central nervous system with the *important exception of cerebrospinal syphilis*. Further, the history demonstrates that the course of the disease is not always slowly progressive and uneventful as was at one time supposed, but is more often interrupted by acute and unexpected disturbances. In more than half (54·3 per cent.) of our cases the onset was comparatively sudden, while in more than two-thirds (68·6 per cent.) some of the symptoms, but not necessarily the initial disturbance, came on acutely. In 85·7 per cent. of our cases the disease had run a discontinuous course, the symptoms pointing now to this and now to that locality of the brain or cord, appearing in an irregular and haphazard manner, and at greatly varying intervals of time. Remissions or quiescent periods, often of many years' duration, alternate with periods marked by the more or less rapid development of fresh disturbances in a manner which is bewildering in so far as it defies accurate anticipation.

We have taken care to select for the purposes of this investigation only those cases which presented evidences of *recent or progressive*

lesions. This selection excludes from the present review two types of case, first the non-progressive case, i.e, patients in whom the disease is in a state of arrest, the condition having remained completely stationary for several months or years, and secondly the so-called "cures," i.e., those in whom no trace remains of a previous pathological condition, as judged by an entire absence of both symptoms and physical signs. We wish to emphasize the fact that such cases occur not infrequently, and that patients, especially those in whom the initial disturbance was relatively sudden, may remain in perfect health for months or years at a time (*vide* Case XIX). How long this immunity can last we are not in a position to say, but in view of the fact that the existence of the non-progressive group is generally admitted, together with the circumstance that the initial stages of the disease are frequently overlooked or wrongly diagnosed, it seems possible at any rate that more cases than is commonly supposed recover from their early lesions and remain well permanently.

Although we desire to lay particular stress on the acute features of the disease, it must not be forgotten that a small number of cases begin insidiously and progress insidiously, while many cases also, which in the early stages were characterized by exacerbations and remissions, eventually assume a more chronic character and progress slowly downhill without new incidents. No hypothesis of the pathogenesis of disseminated sclerosis is satisfactory which fails to take into account the different clinical forms which the disease assumes in different individuals, or in the same individual at different stages of its development.

Clinically, therefore, disseminated sclerosis reveals itself in a haphazard series of relatively acute disturbances occasioned by focal lesions distributed at random both in the brain and cord, appearing at irregular intervals, and showing in their early stages a general tendency to improvement.

Sites of election have long been recognized in this disease, and it is well known that the white matter of the cord, as opposed to that of the brain-stem, is much more commonly affected than the grey. In consequence of this tendency to localize itself in certain areas, the disease presents clinical features which are said to be "typical." Nevertheless no single symptom or sign (e.g., "scanning speech") is of itself characteristic of the condition, but rather a combination of such symptoms and signs. We would further point out that a condition so kaleidoscopic in its symptomatology and clinical course as is

disseminated sclerosis seems peculiarly ill adapted for classification into types and sub-types so dear to the heart of many continental writers.

In the accompanying table is set forth the relative frequency with which certain symptoms and signs were found in our thirty-five cases. Besides indicating the multiplicity of the symptomatology of the disease, it shows that at any rate in the earlier stages the clinical picture departs widely from most text-book descriptions.

NUMBER OF CASES EXAMINED: THIRTY-FIVE.

	Number of cases	Percentage of total
Discontinuous course	30	85·7
Chronic progressive course	5	14·3
Paræsthesiæ	29	82·6
Loss or impairment of deep sensation	23	65·7
Loss or impairment of vibration in lower limbs (23 cases examined)	14	60·8
Disturbance of cutaneous sensibility	11	31·4
"Useless arm"	14	40·0
Extensor plantar response	32	91·4
,, bilateral	27	77·1
,, unilateral	5	14·3
Absent abdominal reflexes (bilateral)	27	77·1
,, ,, ,, (unilateral)	1	2·9
Spastic paraplegia	16	45·7
Sphincter disturbance	25	71·4
Nystagmus	26	74·3
Intention tremor of arms	15	42·6
Cerebellar inco-ordination of arms	15	42·6
Cerebellar gait	18	51·4
Tremor of unsupported head	13	37·1
Ataxic dysarthria	10	28·6
Pallor of optic disks (33 cases examined)	19	57·6
,, ,, ,, (bilateral)	15	45·5
,, ,, ,, (unilateral)	4	12·1
Sudden amaurosis	7	20·0
Severe bilateral visual failure	3	8·6
Diplopia	12	34·3
Rotatory vertigo	18	51·4
Defective emotional control	18	51·4

The most common symptom was paræsthesia, present in 32·3 per cent. of the cases. Although often transient, these subjective disturbances are absolutely definite and constitute one of the most characteristic features of the disease. They may be the first evidence of the pathological process, and although varying in their character and locality are rarely absent at one or other period of the illness. They are variously described as "tightness," tingling, numbness, boring pains (never lancinating pains as in tabes), aching, "rheumatism," "like water trickling down the skin," "like something tickling," coldness, "as if my legs were being scorched in front of a fire," pins and needles, "as if my body and legs were in plaster," &c. These

sensations were referred to the trunk and (or) limbs, and in two cases to the tongue, but were never associated with visceral disturbances such as occur in tabes. Except that they are far less frequently restricted to the peripheral segments of the limbs, they are comparable in every particular to the paræsthesiæ which form so notable a feature in the symptomatology of toxic degeneration of the posterior columns of the cord associated with pernicious anæmia (subacute combined degeneration), and they are to be regarded as evidence of morbid changes in the posterior columns.

Evidence of disturbance of deep sensibility in one or more limbs was obtained in two-thirds (65·7 per cent.) of our cases. Unfortunately vibration was not tested in every case, otherwise the proportion would probably have been greater. In the twenty-three cases in which vibration was tested, in fourteen (60·8 per cent.) loss or impairment of this quality of sensation was demonstrated in one or both of the lower extremities. We are, therefore, unable to agree with the statement current in most text-books that objective disturbances of sensation are rare in this disease. On the contrary we regard disturbance of deep sensation (i.e., compasses, tuning-fork, stereognosis, passive position and movement) as one of the most characteristic signs of the disease, and as evidence of involvement of the posterior columns of the spinal cord or of their upward continuations.

With regard to disturbance of cutaneous sensibility we agree with other authors that it is relatively uncommon; in our series it was present in less than one-third of the cases (31·4 per cent.).

Before leaving the subject of sensory disturbances we should like to draw attention to a symptom-complex, first described by Oppenheim, which may be called the "useless arm." The condition usually develops rapidly in the course of a few hours or days, with or without preliminary warnings in the shape of paræsthesiæ. As a rule it is unilateral, and the expression used by the patient to describe the condition is almost invariably the same, viz., "the arm is useless." Objectively there is profound loss of deep sensation in one of the upper extremities, e.g., no threshold to compasses, complete astereognosis, no response to vibration, and wild sensory ataxia with abolition of the sense of passive position and movement sometimes complete even at the shoulder-joint. Hence the patient says: "I lose my arm in bed," or "The arm has an existence apart from me." The limb is not paralysed, and provided the patient gazes fixedly at the arm when each muscle group is tested there is no loss of power, but

with closed eyes there is an apparent paresis, which is however entirely due to the falling out of afferent impulses from muscles and joints and a consequent inability properly to apply muscular power.

This curious condition may be the first and only evidence of disseminated sclerosis; in the present series it was not infrequently associated with nystagmus, more rarely with a transient impairment of tactile sensibility in the affected limb, and never with bulbar symptoms. The condition of the arm improved in every case, and cleared up entirely in Cases XIX and XXXIV. We regard the condition as the result of an acute but not necessarily destructive lesion in the external portion of the homolateral posterior column of the upper cervical cord. It occurred in 40 per cent. of our cases, i.e., in nearly the same proportion as two of the conditions which are commonly described as "typical" of the disease, namely, spastic paraplegia and intention tremor.

Evidence of interference with the pyramidal system of fibres was obtained in a large majority of our cases. Thus an extensor plantar response was present in 91·4 per cent., bilateral in 77·1 per cent., and unilateral in 14·3 per cent., while the abdominal reflexes were absent on both sides in 77·1 per cent. Spastic weakness of both legs sufficient to warrant the description of spastic paraplegia obtained in less than half the cases (45·7 per cent.). In only two cases was an atrophic paralysis present (Cases II and XIII).

Inco-ordination of movement, apart from that due to the falling out of afferent impulses from deep structures, was present in approximately half the cases. In a disease such as disseminated sclerosis where motor and sensory tracts are prone to be affected simultaneously at different levels of the cerebro-spinal axis, it is not always easy to identify precisely what elements of disordered co-ordination are due respectively to paresis, to loss of deep sensibility, or to interference with the cerebellar system. For example, the intentional tremor, which has so long held a prominent place in the symptomatology of the disease, is in many respects similar to, but is nevertheless not quite the same as, the rhythmical tremor associated with subthalamic lesions. The latter is a pure tremor initiated by the withdrawal of support from the affected limb, while the former is best demonstrated in the execution of some voluntary movement, and is a combination of tremor and inco-ordination. Hence we are inclined to regard the intention tremor of disseminated sclerosis as the result of

destruction of cerebello-rubral fibres and of certain other cerebellar connections in addition.

Definite evidence of cerebellar inco-ordination in one or more limbs, apart from intention tremor, was obtained in eighteen cases (51·4 per cent.). True intention tremor of one or both arms was present in 42·6 per cent., and a nodding to-and-fro tremor of the unsupported head in 37·1 per cent. Ataxic dysarthria on the other hand occurred in only one-fourth of the cases (28·6 per cent.).

Attacks of rotatory vertigo, usually sudden in onset and offset, but sometimes persisting for days or weeks at a time, were common at some period of the disease (51·4 per cent.). It is interesting to note that although tinnitus was associated with these attacks in a few cases, in no instance was any diminution of auditory acuity demonstrable at the time of examination, a fact which points to the vertigo being central, and not peripheral, in origin.

Sustained nystagmus in one direction or another, usually horizontal, was present in 74·3 per cent.

Regarding ataxic dysarthria, nystagmus, vertigo, nodding tremor of the head, intention tremor of the arms, and inco-ordination of the limbs (apart from sensory defects) as evidence of disturbance of the cerebellar system, we believe that there are good grounds for assuming that the lesions underlying these phenomena are situated in a vast majority of the cases in the brain-stem and mid-brain. The assumption is supported by the circumstance that some or all of these disturbances tend to be combined in the same individual.

For example, in eight of the ten dysarthric patients there were also present tremor of the head, intention tremor, and reeling gait, while all the cases with head tremor, except one, presented evidence of cerebellar inco-ordination in arms or legs, or in both.

Diplopia, usually transient, occurred in a third of the cases (34·3 per cent.), but evidence of involvement of cranial nerves other than the optic and oculo-motor group was rare. In no case did the pupillary reactions show any departure from the normal.

Disturbances of the visual mechanism have long been recognized as being one of the most frequent and characteristic features of disseminated sclerosis. Pallor of the optic discs was observed in nineteen cases out of thirty-three in which they were examined (57·6 per cent), bilateral in 45·5 per cent., unilateral in 12·1 per cent. The pallor sometimes involved the whole disc, but more commonly the temporal half only, and in a great many cases it was associated

with normal visual acuity. A history of sudden amaurosis in one eye with subsequent improvement in vision (retro-bulbar neuritis) was obtained in 20 per cent., while severe bilateral visual failure of sufficient degree to be termed disabling was present in only three patients (8·6 per cent.). Scotomata were present in several cases, but the details in this connection were not fully investigated.

Partial or complete loss of control over the bladder was noted in 71·4 per cent. of cases, and when not associated with a paraplegic condition was regarded as evidence of disease in the lumbo-sacral region of the cord.

As regards the mental condition, a majority of the patients were above rather than below the average intelligence. Definite loss or impairment of emotional control, with which was frequently associated an unduly sanguine temperament, was present in half the cases (51·4 per cent.), a defect which permitted the patient to regard his or her condition with indifference or even with amusement.

Loss of consciousness occurred in one patient only.

In no case were any indications observed pointing to disease of the thoracic or abdominal viscera, or to the hæmopoietic system.

The family and past histories failed to throw any light on the ætiology of the disease.

Sex.—There were twice as many females as males (65·7 to 34·3 per cent.).

Age.—The average age of onset was 24·6 years, the youngest case being 16, and the oldest 39 years old. The average age at the time of observation was 28·6 years.

Duration.—The disease had lasted four years on an average, the shortest case being three weeks, the longest fourteen years. Of the two fatal cases one lasted four years and the other thirteen months.

Summary of clinical study.—Disseminated sclerosis is a disease of young adult life, occurring in healthy individuals, characterized in a large majority of cases by an intermittent course, punctuated at irregular intervals by relatively acute exacerbations with subsequent periods of improvement and quiescence. The exacerbations consist either in the appearance of new symptoms due to lesions in fresh localities, or else in an accentuation of symptoms previously experienced, but at the time quiescent. In a small proportion of cases the disease pursues a chronic progressive course from the outset, with a gradual increase in the intensity of existing symptoms and a relative infrequency of new ones.

There is abundant clinical evidence of the random dissemination of the lesions throughout the brain, brain-stem, and cord, and of the involvement in the cord of the white matter rather than the grey. The general clinical course, especially in the case of single acute lesions, is highly suggestive of a localized acute, or subacute, inflammation. There is no evidence of thrombosis or embolism of large vessels, nor is there anything in the clinical study of our cases suggestive of meningeal inflammation or increased intracranial pressure.

Investigation of Two Fatal Cases.

Case I.—Girl, aged 19. Admitted August 12, 1913. Died November 24, 1913 (National Hospital, Queen Square). Good family and past history.

Aged 15: She suddenly lost power and feeling in the left upper extremity; the power soon returned but the hand was "useless" for nearly three months, after which it got perfectly well.

Aged 16: Sudden attack of pain in the right eye which rapidly became blind; examination revealed a retro-bulbar neuritis with profound but not complete loss of vision. Two months later the right optic disc was passing into atrophy and she could count fingers at 3 ft.

Aged 17: Numbness of the right thigh followed by weakness of the right leg and inability to walk. She was admitted to the West London Hospital where she rapidly developed incontinence of urine and fæces, with occasional retention requiring catheterization. She also had diplopia and attacks of rotatory vertigo. On discharge from hospital four moths later she walked "all over the place," and her head and her hands shook so much that she could hardly feed herself. In this condition she remained for eighteen months troubled with fleeting paræsthesiæ, diplopia, vertigo and headache.

Aged 19: One month ago the left arm became suddenly "useless," so that she could not feel what she had in her hand; this was followed a few days later by a similar condition of the right arm.

One week later a further series of symptoms developed: (i) persistent vomiting and constant vertigo, an ever present feeling of herself and her surroundings rotating, worse on movement of head and eyes, "nothing keeps still"; (ii) diplopia; (iii) inability to walk or sit up in bed; (iv) loss of emotional control; (v) retention of urine.

A week later (i) she lost all sphincter control, unconscious of "call" and of the passage of excreta; (ii) the legs became completely paralysed and numb: "I do not know that I have legs except for the pains in them;" (iii) speech became slow and stammering, and (iv) she had attacks of dyspnœa, and (v) difficulty in swallowing.

On admission (August 12, 1913).—Good physique and nutrition. Temperature 99·2° F., pulse 96. Sleepy expression (ptosis), with head turned to right.

Visceral examination negative; severe cystitis present.

Mental.—Distracted, inattentive and irrational. Wishes to die and the next moment evinces confident hopes of recovery. Lacking in reserve and emotional control.

Wassermann reaction (*blood*) negative.

Speech.—No aphasia. Cannot raise voice above a whisper, articulation jerky, slow and tremulous.

Vision.—Acuity, counts fingers at 3 ft. on right, $\frac{6}{36}$ on left. Fields: gross constriction with central scotoma in right eye, and no colour vision; moderate constriction in left. Both discs very white, edges clear, pigment disturbed; changes right more than left.

Hearing.—Normal. Constant vertigo; turning head to left causes a movement of objects from left to right.

Cranial nerves.—iii, iv, vi. Wide pupils, right more than left; the right is sluggish to direct light but reacts well consensually, left normal. Both react well to accommodation. Diplopia, paralysis of right superior rectus and left internal rectus. Ptosis, right more than left, with frontalis overaction. Constant jelly-like nystagmus with eyes at rest. On conjugate deviation both to right and left there is a slow horizontal nystagmus of large amplitude, and a rotatory nystagmus on looking up and down. v, vii, xii normal, except for slight paresis of left lower face. ix, x, xi: palate immobile, reflex absent. Dysphagia. Dysarthria.

Motor.—Head and neck: No paralysis; tremor when unsupported.

Upper limbs: (*a*) Right: General weakness, especially of extensors; normal tone, well-marked intention tremor and dysmetria. (*b*) Left: Hemiplegic attitude, spastic, movements at all joints minimal, extensors weaker than flexors, no wasting.

Trunk: Cannot move in bed. Intercostal movement below sixth rib is poor and abdominal muscles are paralysed.

Lower limbs: Right and left: Complete spastic paraplegia in extension with occasional involuntary flexor spasms.

Sensory.—(i) Subjective: Severe boring paroxysmal pains in abdomen and legs. Feels slight discomfort with distended bladder. (ii) On examination: Questionable impairment of tactile sensibility in both hands. Pain and temperature normal in upper limbs. Complete astereognosis in both hands. Profound loss of passive position and movement whole of left upper limb, considerable loss in right hand. Below the seventh rib there is an almost complete anæsthesia to all forms, both superficial and deep; a sharp prick or deep pressure sometimes gives rise to indefinite pain which cannot be localized.

Spinal column.—Healthy.

Sphincters.—Rectum: Complete incontinence; feels neither "call" nor passage. Bladder: Feels neither "call" nor passage, retention alternates with incontinence.

Reflexes.—All tendon-jerks brisk. Abdominals all absent. Extensor plantar response, right and left.

Treatment.—Bladder—wash twice daily.

Progress (September 9, 1913).—Patient has had frequent attacks of respiratory embarrassment, with very shallow movement of chest, cyanosis, restlessness, but no stridor. There is a curious irregularity of the respiratory rhythm. Increasing dysphagia, vomiting and mental deterioration.

September 15, 1913: The upper limit of complete anæsthesia and paralysis now reaches the fourth rib; the paraplegia is now in flexion rather than in extension. Urine is now free of pus.

September 25, 1913.—Irregular pyrexia the last few days; trace of pus in urine. Regurgitation of fluids through nose.

October 10, 1913: Pyrexia persists. Commencing sacral bed-sores with emaciation and cachexia. Less dysphagia, dyspnœa and vertigo.

November 18, 1913: General condition much worse: profound wasting and cachexia with rapid extension of bed-sores.

November 24, 1913: Died.

Pathological investigation.—The patient was lumbar punctured on September 30, 1913, and again on October 27, 1913, and the cerebrospinal fluid examined by the same methods and with the same results in each case, as follows:—

Cerebrospinal fluid quite clear; no cells and no excess of protein; Wassermann reaction negative. The fresh fluid was precipitated with absolute alcohol and the centrifugalized deposit stained with Giemsa and examined microscopically with negative results.

The fresh fluid was centrifugalized and the deposit added to four tubes of Noguchi's medium. Of these, two tubes remained sterile, while in the other two a long-chained streptococcus was grown which was Gram-positive and grew well in ordinary media with diffuse turbidity. The deposit from all four tubes after incubation was stained with Giemsa and examined microscopically; in each case small granular bodies were observed, but precisely similar bodies were found in the deposit of uninoculated tubes.

No animal inoculations were carried out with the fresh cerebrospinal fluid.

A post-mortem examination of the patient's body was carried out twenty hours after death by Dr. S. A. Kinnier Wilson, who kindly gave us every facility for our investigations. Before removal of the organs cultures were made from the frontal regions of the brain on both sides and from the cord. A long-chained streptococcus was grown from each site, which acidified litmus milk and lactose, but did not affect raffinose, inulin or mannite.

Portions of the patient's brain and cord were removed with all reasonable precautions and ground in a mortar. Films of the suspension

thus obtained showed diplococci and streptococci, but no spirochætes were found by the dark-ground illumination method. The suspension was then filtered through a Doulton candle and on November 26, 1913, injected under general anæsthesia into rabbits as follows :—

Rabbit 1.—Trephined: 0·25 c.c. of suspension injected intracerebrally and 5 c.c. intraperitoneally. The animal remained in perfect health and was killed nine weeks later. Post-mortem examination revealed no disease of the internal organs. Smears were made from the cerebral and spinal membranes and stained with Giemsa with negative results. The pons and mid-brain were examined histologically and found to be healthy.

Rabbit 2.—Trephined: 0·25 c.c. of suspension injected intracerebrally. The animal remained in perfect health and was killed five months later. Histological examination revealed no disease in brain or cord.

Rabbit 3.—Injected intraperitoneally with 8 c.c. of suspension. No immediate or remote results, and the animal was well five months later.

The histological examination of the patient's brain and cord were unfortunately very incomplete, and the notes concerning it have been lost. Both brain and cord were riddled with sclerotic areas, one large one involving the whole transverse area of the cord in the upper thoracic region. In the lower half of the pons very little normal tissue remained. A perivascular round-cell infiltration was a prominent feature of the diseased areas.

Case II.—Male, aged 26. Admitted November 19, 1913. Died February 20, 1914. Family and past history unimportant. Ten months ago (January 6, 1913) he "suddenly came over sick and giddy" but was well in three days. Three weeks later the same thing happened, and his legs became so weak that he could not walk and his hands were unsteady. He was admitted to the London Hospital where he improved, and after seven weeks he could write a letter and walk without support. On discharge he began to notice transient numbness and tightness in his left leg and arm, "as if my leg would burst." These paræsthesiæ persisted, but no further symptoms developed until August, when his sight began to fail and his left eye became rapidly blind. In September his walking got much worse and he had frequent falls; he also had difficulty in voiding his urine, and towards the end of the month he developed incontinence of both bladder and rectum.

Four weeks ago his left arm became much weaker and more unsteady, his left leg almost paralysed, his speech almost unintelligable, and his memory began to fail.

On admission (November 19, 1913): Poor physique. Temperature 100·4° F., pulse 80.

Visceral examination.—Negative. Urine normal.

Wassermann reaction (blood).—Negative.

Mental.—Intelligent but apathetic. Normal emotional tone.

Speech.—No aphasia. Articulation slow, scanning, tremulous and ataxic.

Vision.—Acuity: Left $\frac{6}{60}$, right $\frac{6}{18}$. Left optic disc very pale, edges fluffy, some disturbance of retinal pigment; consecutive atrophy. Right optic disc pale, especially on temporal side; primary atrophy.

Hearing.—Normal. No vertigo now, or tinnitus.

Cranial nerves.—Normal except for weakness of right lower face, and horizontal nystagmus of wide range on looking to right and left.

Motor.—Head and neck: Nodding tremor of unsupported head.

Upper limbs: (*a*) Right, power everywhere subnormal, tone a little increased, well-marked intention tremor and slight sensory ataxia. (*b*) Left, muscles of forearm and hand weak and wasted, with diminution of faradic irritability, extreme intention tremor and sensory ataxia.

Trunk: Cannot sit up without use of hands.

Lower limbs: Both weak and spastic, left more than right; all flexors weaker than extensors. Legs in extension with occasional flexor spasms in left leg. Musculature poor. Legs tremulous.

Sensory.—Profound loss to pin-prick and temperature to right of mid-line below umbilicus. Tactile sensibility greatly impaired whole of left lower limb. Vibration completely abolished in lower limbs and pelvis and much impaired in hands (left more than right).

Compasses: No threshold obtainable in palms or soles.

Complete astereognosis in both hands.

Passive posture and movement: Profound loss distally in upper limbs (left more than right), considerable loss in lower limbs (left more than right).

Spinal column.—No evidence of disease.

Sphincters.—Complete incontinence of urine and fæces; feels neither call nor passage.

Gait.—Cannot stand alone; very tremulous; no control over legs.

Reflexes.—Left supinator jerk absent, all other jerks very brisk. All abdominals absent. Extensor plantar response, right and left.

Progress (December 18, 1913).—Condition deteriorating. Dysarthria is now so profound that he is barely intelligible. Mild irregular pyrexia; bed-sore developing over sacrum; urine normal.

January 15, 1914: Legs are now completely paralysed; paraplegia in flexion.

February 13, 1914: Whole of left face and left side of palate paralysed. Dysphagia has developed with regurgitation of fluids through nose. Complete loss of upward movement of both eyes.

Still slight irregular pyrexia. Bed-sore has increased, but is not deep and is fairly clean. No cystitis.

February 20, 1914: Died.

Pathological investigation.—The patient was lumbar punctured on December 1, 1913, and on December 18, 1913. The cerebrospinal fluid was quite clear, there was no excess of globulin, and the Wassermann reaction was negative. In the fluid from the first puncture no cells were found, while in the second there was a very slight excess of small lymphocytes.

On December 1, 1913, two rabbits were injected intraperitoneally, one with 15 c.c. and the other with 10 c.c. of the patient's unheated blood-serum without immediate effect. Two days later fresh cerebrospinal fluid was obtained from Case III (from which a streptococcus had been previously grown; *vide infra*), and 0·25 c.c. of the centrifugalized deposit was injected intracerebrally into both rabbits. Both animals remained well; one was killed six weeks later and no histological or naked-eye changes were found in the brain or cord, the other was alive and well three months afterwards.

Cultures of the fresh cerebrospinal fluid of Case II, both aerobic and anaerobic, remained sterile, and examination of the stained centrifugalized deposit was negative. On December 18, 1913, two rabbits were injected intracerebrally with 0·5 c.c. of the centrifugalized deposit of fresh cerebrospinal fluid. Both remained well; they were killed three and four months later respectively and no lesions, naked-eye or microscopic, were found in the brain or cord.

Post-mortem examination of Case II (six hours after death).—No naked-eye evidence of disease in internal viscera. Numerous sclerotic foci were present in the cerebral cortex, basal ganglia, periventricular tissue, pons, medulla, and spinal cord (especially in cervical region); none were visible in the mid-brain. No naked-eye evidence of meningitis. Portions of the brain and cord were ground up in a mortar with physiological saline, filtered through a Berkefeld V-candle, and three hours after removal of the tissue from the body 0·5 c.c. of this filtrate was injected intracerebrally into a rabbit and 4 c.c. intraperitoneally. Three days later another 7 c.c. of filtrate was injected intraperitoneally. The animal remained well and was killed four and a half months later; nothing abnormal, naked-eye or histologically, was found in the brain or cord.

Histological.—Both kidneys showed chronic tubal change.

Sections of brain and cord stained by the Weigert-Pal method gave the following results:—

Numerous small foci of myelin sheath destruction were found scattered throughout the cerebral hemispheres both in the cortex and

adjacent white matter, especially in the anterior half of the brain. Extensive sclerotic patches were present in the basal ganglia and in the periventricular regions.

Subthalamic region: The red nucleus on either side was involved in a patch of sclerosis.

Pons: numerous sclerotic foci were scattered throughout the pons, especially round the fourth ventricle, in the region of the right middle cerebellar peduncle, and both facial nuclei.

Medulla: numerous foci were present, right more than left; the region of the right restiform body was occupied by an area of particularly dense sclerosis.

Spinal cord: (i) Upper cervical: sclerotic areas occupied the central and external portions of both posterior columns, and a large focus involved the left antero-lateral region and anterior horn.

(ii) Lower cervical: sclerotic foci present in both anterior columns, in the crossed pyramidal tract on the right side, and in the posterior columns on both sides.

(iii) Mid-thoracic cord: both posterior columns involved throughout in an area of sclerosis. On the right side the lateral column, and on the left the antero-lateral column were occupied by areas of dense sclerosis, which invaded the anterior horn on the left side.

(iv) Lumbar: whole transverse area, except the anterior columns, occupied by dense sclerosis.

Cerebellum, spinal roots, and ganglia—not examined.

Sections stained with Giemsa showed that the patches of sclerosis were not all sharply defined from the normal tissue. This lack of definition was greatest in the areas which appeared to be fresh; in these, especially in the cortex and brain-stem and to a very much smaller extent in the cord, the nerve cells showed chromatolysis and indistinctness of outline, and glia-cell proliferation was a prominent feature. In the older areas the gliosis was more intense and characterized by proliferation of glia fibrils.

In the leptomeninges and throughout the brain and cord a perivascular infiltration with round cells and endothelial cells was present. This change was particularly noticeable in the fresh areas of sclerosis, but was not entirely absent in areas which were of long standing.

Investigations carried out in Thirty-three Non-Fatal Cases.[1]

(1) *Examination of Cerebrospinal Fluid.*

The examination comprised the following points:—

(*a*) Cytology (all cases).

(*b*) Globulin reaction (all cases).

(*c*) Wassermann reaction (all cases).

(*d*) Microscopical examination of deposit obtained by precipitating the fresh cerebrospinal fluid with absolute alcohol, stained with Giemsa (all cases).

(*e*) Anaerobic cultivation (27 cases).

(*f*) Microscopical examination of deposit in Noguchi tubes after inoculation with cerebrospinal fluid and incubation (25 cases).

(*g*) Aerobic cultivation (19 cases).

The colloidal-gold reaction was not tested in any case.

The results obtained were as follows:—

(*a*) No excess of cells was obtained in any of the 33 cases. Occasionally one lymphocyte was found in the centrifugalized deposit but in the vast majority of cases no cells of any kind were present. It will be remembered that in one specimen of cerebrospinal fluid from Case II a slight lymphocytosis was present.

(*b*) Globulin reaction (tested by half saturation with ammonium sulphate); a positive reaction was present in Case XXXIV, a very slight reaction in Cases XXVII, XXXI and XXXV, and a negative reaction in the remaining 29 cases.

(*c*) The Wassermann reaction was negative in every case, both in the blood and the cerebrospinal fluid.

(*d*) Deposit obtained by precipitation with absolute alcohol: in Case VIII examination of the deposit stained with Giemsa revealed numerous small bodies resembling cocci. [In two cases (XXXIV and XXXV) small granules resembling fat were observed by the dark-ground illumination method; similar bodies have been observed in the cerebrospinal fluid and brain emulsions of cases of encephalitis lethargica and uræmia and are probably fragments of altered myelin. With these exceptions this method yielded negative results.]

(*e*) Anaerobic cultivation. The following media were used:—

(i) Noguchi's fluid medium (ascitic fluid + fresh rabbit's kidney, in 23 cases (III to XXI, XXX and XXXI, XXXIV and XXXV).

[1] For clinical details of cases *vide* Appendix.

(ii) Ascitic fluid + human red cells in three cases (XXIII to XXV).

(iii) Noguchi solid medium (agar + rabbit's kidney) in two cases (XXX and XXXI).

(iv) Ascitic fluid only in Case XXII.

In twenty-one cases all the inoculated tubes remained sterile. In three Cases (IV, XIX, XX) a diphtheroid bacillus was grown; in Cases IV and XIX the same bacillus also grew in aerobic cultures. The bacillus grown anaerobically in Case XX was non-pathogenic to guinea-pigs.

Case III, from which a streptococcus was grown, merits a more detailed description. The patient was a girl, aged 18, and the illness dated back to just over a year previously when she was suddenly seized with pain behind the eyes and failure of vision. The vision improved somewhat, but in the course of the next four months she developed successively weakness of the trunk muscles, tremor of the left arm, loss of sphincter control, weakness of the right leg and then of the left. At the time of our investigations she was rather rapidly getting worse and becoming more paralysed below the waist; there were however no acute exacerbations, no bed-sores, cystitis, or pyrexia.

Lumbar puncture was performed on three occasions as follows:—

(i) September 30, 1913. The centrifugalized deposit of cerebrospinal fluid was added to four Noguchi tubes, of which two remained sterile, while in the other two a pure growth of a Gram-positive, long-chained streptococcus appeared, which grew well in ordinary media with diffuse turbidity. Three rabbits were then inoculated intracerebrally with 0·5 c.c. of a twenty-four hours' growth of the streptococcus. Two days later two animals were dead, and examination revealed frontal abscesses, the pus from which contained long-chained streptococci in large numbers. The third animal was ill two days after inoculation, but recovered rapidly. It was killed eight weeks later, and post-mortem examination revealed nothing abnormal in brain, cord, or meninges, and cultures from the meninges remained sterile.

Intraspinal injection into a rabbit of 1·5 c.c. of fresh cerebrospinal fluid was followed by no immediate or remote effects, and histological examination of the animal's cord ten weeks later revealed nothing abnormal.

(ii) October 27, 1913. Patient was again lumbar punctured, but on this occasion all anaerobic and aerobic media remained sterile.

(iii) December 3, 1913. Lumbar punctured. Two rabbits, both of which had two days previously received an intraperitoneal injection of the unheated blood serum of Case II (fatal case), were injected intracerebrally with 0·25 c.c. of the centrifugalized deposit of cerebrospinal fluid. In neither animal was any effect produced.

The streptococcus grown from the first sample of cerebrospinal fluid in this case resembled that grown post mortem from the brain of Case I in both its morphological and cultural characteristics.

(*f*) Examination of Noguchi deposit. Films were stained with Giemsa and searched for parasites with negative results. In several cases small granular amorphous bodies were found, which were particularly numerous in Case XXI. In this case 10 c.c. of the Noguchi fluid were injected intraperitoneally into a rabbit which two weeks previously had received 2·5 c.c. of the patient's cerebrospinal fluid along the course of one sciatic nerve plus 5 c.c. of the patient's blood serum intraperitoneally. The animal however remained well.

Similar granular bodies were frequently found in the deposit from Noguchi tubes which had not been inoculated with cerebrospinal fluid.

(*g*) Aerobic cultivations: various media were used, litmus milk, inulin, inulin plus serum, Besredka with and without human red cells, &c.

In Cases IV and XIX a diphtheroid bacillus was grown, and from Case XIII a pure culture of *Staphylococcus albus* was obtained, which we regard as a contamination.

With these exceptions the cultures all remained sterile.

(2) *Animal Experiments (Thirteen Cases).*

Rabbits were employed in every case, and in a few instances guinea-pigs in addition. All animal experiments were conducted under general anæsthesia and with strict aseptic precautions. We consider the use of a general anæsthetic important in order to obviate the traumatic palsies, especially of the hind limbs, to which rabbits are particularly susceptible; these palsies which occur in animals improperly treated have been a fruitful source of error in the past.

To the experiments in connection with the two fatal cases in which intracerebral injections of suspensions of cerebral and cord tissue were effected, reference has already been made. The intracerebral route was also used in Cases III, XXVII and XXVIII, the material injected in each case being 0·25 c.c. of the centrifugalized deposit of fresh cerebrospinal fluid.

Injections were made of from 2·5 to 5 c.c. of fresh cerebrospinal fluid along the course of the sciatic nerve in Cases XIX, XX, XXI, XXVI and XXVIII. In the first three of these cases intraperitoneal injections of from 5 to 10 c.c. of the patient's unheated blood serum were given simultaneously, and in Case XXVIII an intracerebral injection (0·25 c.c.) of centrifugalized cerebrospinal fluid.

In Case III an intrathecal injection of 1·5 c.c. cerebrospinal fluid was given, in Case XXV an intravenous injection of 2 c.c., and in Case XXIX an intratesticular injection of 3 c.c.

In none of the above cases were the injections followed by any immediate or remote effects; all the animals remained in good health, and in those that were killed at some subsequent period no lesions, naked-eye or histological, were found in the internal viscera, meninges, brain or spinal cord.

In Cases XXXIV and XXXV the intra-ocular route was adopted. In each case a rabbit was inoculated with 0·25 c.c. of centrifugalized deposit of cerebrospinal fluid withdrawn from the patient two hours previously. Six days later the rabbit inoculated with cerebrospinal fluid from Case XXXIV was disinclined to move and its hind limbs were stiff. The following day the weakness and stiffness of the hind limbs were more obvious, the animal responded slowly when pricked, its gait was laboured and there was some "shivering" of the muscles in the lumbar region. Two days later the animal had completely recovered and is alive and well at the time of writing. Six days after injection the animal from Case XXXV showed an exactly similar condition, but the weakness of the hind limbs was rather more pronounced, and the limbs were actually dragged along without being definitely paralysed. After persisting for two or three days the disability completely disappeared and the animal has remained well ever since.

Two guinea-pigs injected intraperitoneally with fresh cerebrospinal fluid from Cases XXXIV and XXXV remained well.

Summary of animal experiments and bacteriological investigations.—It will be seen from the above experiments that in spite of a variety of routes employed for our injections we failed to produce in rabbits any condition of ill-health, with the exception of a transient stiffness of the hind legs in two animals, by inoculating them with the fresh cerebrospinal fluid and blood-serum of patients suffering from disseminated sclerosis, or by inoculating them with fresh, filtered suspensions of the brain and cord of patients recently dead of the isease.

In other words we have entirely failed in our attempts to transmit disseminated sclerosis to animals.

As regards our bacteriological findings a long-chained streptococcus was grown in two cases, from the cerebrospinal fluid of Case III, and from the cerebrospinal fluid during life and from the cerebral hemispheres after death in Case I. In the latter case (Case I) owing to cystitis and bed sores the patient had been in a profoundly septic and cachectic condition for six weeks prior to her death, and the bacteriological result may reasonably be thus explained. Case III however had neither cystitis, bed-sores, nor pyrexia, and the presence in the cerebrospinal fluid of a streptococcus, cultures of which on intracerebral injection into rabbits caused death with the formation of frontal abscesses, was not traced to a septic focus. At the same time, while unable to advance any adequate explanation of the bacteriological finding in this case, we are by no means inclined to regard it as of any significance with reference to the pathogenesis of disseminated sclerosis.

Review of Recent Work on the Pathogenesis of Disseminated Sclerosis.

(1) *Histological. Morbid Anatomy.*

Two exhaustive investigations of the morbid anatomy of the disease have appeared within the past few years.

(*a*) Siemerling and Raecke in 1914 published the results of detailed histological examination of eight cases together with a clinical review of sixty others. They consider that the primary and essential feature of the pathological process is a localized destruction of nervous tissue, the process being closely related to changes in the vessels, which show definite inflammatory phenomena, viz., congestion, perivascular infiltration with small lymphocytes, polymorphs and plasma cells, and in many cases capillary hæmorrhages.

They describe the early changes, best studied in the small, circumscribed patches ("Herde") in the brain, as being characterized by a focal destruction of axis cylinder fibres, with which is associated a considerable destruction of the medullary sheaths. The foci tend to coalesce and the medullary sheath destruction becomes more and more complete. In the cerebral cortex and periventricular region the lesions are grouped according to the distribution of terminal arteries and resemble infarcts, the cortical foci usually having a pial vessel in their centre. Immediately consequent on the destruction of nervous tissue

a marked proliferation of the glia occurs, which acts as scar tissue and helps to protect the tissues from further damage. The early stages of the glia reaction are characterized by a richness of glia nuclei, which later on are reduced in number to be replaced by a thick network of glia fibrils. Associated with the myelin sheath destruction numerous scavenger cells make their appearance, arising mainly from the neuroglia and to a less extent from the blood elements. These cells, which effect the transportation of the products of destruction, are chiefly compound granular cells, and are most numerous in fresh lesions and in the lymphatic spaces outside the vessels. They are never as numerous as in cases of softening due to arterio-sclerosis, and are much scarcer in the cortex than in the white matter, since myelin destruction is negligible in extent in the former as compared with the latter. These cells contain a large, deeply-staining, round nucleus and their protoplasm is frequently packed with fatty granules staining orange-red with scharlach.

Owing to the excessive glia reaction neighbouring foci tend to be bound together in a common sclerotic plaque. Moreover, the individual foci do not pass directly over into normal tissue, but are surrounded by a broad intermediate zone characterized by a pronounced increase of glia nuclei. In these zones the authors observed a tendency to recurrence of capillary hæmorrhages, while the presence in them of plasma cells was regarded as indicating a lighting up of the active process.

Secondary degenerations, as a result of axis cylinder destruction, were found in distant parts of the nervous system, and mingling with the essential focal lesions produce a complicated and confusing histological picture. While, however, axis cylinder destruction is the first stage in the morbid process and is demonstrable before the medullary sheath is affected, the authors admit that the latter change eventually exceeds the former, and they do not entirely oppose the long-accepted view that the axis cylinders remain relatively intact.

The ganglion cells, although more resistant than the nerve-fibres, also show changes when involved in the primary lesions, but the changes were limited to the focal lesions and were never systemic as in general paralysis.

Occasionally the glia over wide areas, and altogether outside the essential focal lesions, undergoes definite proliferation with an abnormal richness of both nuclei and fibrils and a few pathological spider cells. A section of such an area would certainly give the impression of a

primary glia proliferation, but the authors are of opinion that there are in reality no grounds for postulating a primary gliosis, and they explain the appearances by a leakage from the diseased areas into the periphery of a virus or toxin in a concentration too weak to evoke a focal inflammatory lesion, but sufficiently strong to give rise to a diffuse glia reaction.

The peripheral nerves showed inconstant, non-specific, neuritic changes, and the typical sclerotic plaques were strictly limited to the central nervous system and to the glial portions of the cranial nerves and nerve-roots. In correspondence with the inflammatory nature of the whole process meningitic changes were constantly present, e.g., patchy peri-vascular round-celled infiltrations of the pia-arachnoid; plasma cells were also observed in a few cases.

The cerebrospinal fluid was examined in both fatal and non-fatal cases, and is described as showing "usually a slight lymphocytosis and slight increase of globulin." Bacteriological investigation was negative.

The authors consider that the whole anatomical picture is in complete harmony with the clinical one, viz., acute lesions giving rise to acute symptoms which tend to clear up. They conclude that disseminated sclerosis is infective or toxic in origin, that the virus or toxin reaches the central nervous system through the blood-vessels, and they regard the presence of plasma cells as strong evidence in favour of an infective process and most probably a parasitic one.

(*b*) Dawson examined nine cases histologically and came to much the same conclusions as Siemerling and Raecke, although differing somewhat in his interpretation of the histological details. He describes six stages in the development of the essential lesion, viz.: (1) A commencing reaction of all the tissue components and degeneration of the myelin sheath. (2) Glia cell proliferation and commencing fat granule cell formation. (3) "Fat granule cell myelitis." (4) Commencing glia fibril formation. (5) Advancing sclerosis, and (6) Complete sclerosis.

He regards the primary degeneration of the myelin sheath as the most constant and uniform feature of the histological picture, and considers that the relative persistence of axis cylinders and ganglion cells is abundantly confirmed. Secondary degeneration occurs, but affects scattered fibres and not tracts in their entirety.

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He traces the development of the essential lesions from their

earliest stages to the final development of the dense sclerotic areas visible to the naked eye and scattered throughout both brain and cord, and he finds areas of recent and of old disease in the same patient. Almost every diseased area shows evidence of an advancing process; they are either wholly "early" or show a peripheral advancing zone round a condensed centre, giving the impression that the primary process has never quite died down but is gradually extending peripherally.

According to Dawson vascular phenomena are not prominent in the earliest stages; "in its diffusion through the vessel wall the noxa causes no recognizable primary alteration, but there is probably an abnormal permeability and increased transudation of toxic lymph." The first vascular changes are found at, or just after, the stage of "fat granule cell myelitis," and are secondary to the resorption of the fatty products of destruction; this in time is followed by a proliferation of all the cell elements of the adventitia, and later by a modified infiltration of small round cells and a few plasma cells. Finally as the tissue condenses the vessel walls become thickened and undergo hyaline degeneration.

The cranial nerves and spinal roots are frequently involved in the glial portion of their extra-medullary course, but the meninges show no constant or specific changes.

While not attempting to explain the irregular distribution of the lesions, Dawson considers that the sites of predilection are "probably related (*a*) to the vessels; to the terminal ramifications of end-arteries, e.g., on the ventricular surfaces, and to the points where vessels break up, e.g., in the transition zone between white and grey matter both in the central and cortical grey matter, and (*b*) to areas where much glia is normally present, e.g., the peri-ventricular and peri-central tissue, the optic chiasma, the postero-median and para-median septa, the marginal glia zone, and the perivascular glia layer."

After discussing the somewhat different views as to what should be accepted as the histological criteria of "inflammation" when it affects the central nervous system, he concludes by regarding disseminated sclerosis as a subacute inflammatory disease, i.e., a localized, disseminated, subacute encephalo-myelitis which terminates in areas of actual and complete sclerosis, the causal agent being probably a soluble toxin which is conveyed to the nervous system by the blood-stream. He further points out that the remissions and relapses so characteristic of the disease "necessitate the assumption of the latent

presence of the morbid agent in the body, or, if this is an autogenous toxin, either of its intermittent evolution or of its accumulation from deficient elimination."

Reviewing the views propounded respectively by Siemerling and Raecke and by Dawson, while both sets of investigators regard the histological changes as inflammatory in character, the former look upon the process as acute, while Dawson calls them subacute.

Our own histological investigations are admittedly quite incomplete; but as far as they go they strongly support the view which regards the process underlying disseminated sclerosis as inflammatory in nature; in fact the most conspicuous feature of the sections in Case II was the well-marked perivascular infiltration with round cells and endothelial cells, similar to that met with in cases of encephalitis lethargica, although perhaps not quite so intense. On general grounds we have some difficulty in accepting Dawson's statement that the perivascular changes are absent in the earliest stages of the process, and only appear subsequent to, and as a consequence of, the absorption of the products of myelin destruction and the gradual condensation of the tissues. In Case II these changes were a prominent feature of areas where sclerosis was not yet apparent, and we favour as being more in conformity with the principles of general pathology the interpretation of Siemerling and Raecke, who regard the perivascular reaction as important evidence of the frankly inflammatory nature of the early stages of the morbid process.

(2) *Experimental.*

(*a*) Bullock in 1913 claimed to have transmitted the disease to rabbits by subcutaneous injection of the cerebrospinal fluid of a patient suffering from disseminated sclerosis. Ten rabbits in all were injected; of these four died without paralysis, two remained well, and two became paralysed in the hind limbs three weeks later and then recovered. One animal, twelve days after receiving 2 c.c. of unfiltered cerebrospinal fluid along the course of one sciatic nerve, became paralysed in the hind limbs; killed four days later, an intense cystitis was found, together with some fragmentation of the myelin sheaths in the white matter of the spinal cord, but no Marchi changes. The other animal three weeks after an injection of 1·5 c.c. filtered cerebrospinal fluid became weak in the hind limbs, but afterwards improved and was left with a slight spastic paresis. Six weeks later it was killed, and large areas of degeneration were found throughout the cord in Weigert-Pal

and in Marchi preparations. The verbal description of, and the figures which claim to illustrate, these changes are in our opinion unconvincing, and we are quite unable to accept the author's statement that the changes represent "a complete reproduction of the appearances found in the human subject"

(*b*) Siemerling and Raecke injected rabbits and two apes (*Macacus rhesus*) with cerebrospinal fluid of patients suffering from disseminated sclerosis, with negative results.

(*c*) Kuhn and Steiner injected blood and (or) cerebrospinal fluid of four disseminated sclerosis patients into guinea-pigs and rabbits. From their brief description the diagnosis in Cases III and IV is, in our opinion, open to question. Six guinea-pigs were inoculated intraperitoneally with 1 c.c. of a mixture of blood and cerebrospinal fluid from Case III, of which four developed paralysis and two remained well. Of three guinea-pigs injected with 1 c.c. of blood diluted 1 in 5 from Case IV, one remained well, one was ill four weeks later and recovered, and one became ill five weeks later and died after nine days. Blood-stained cerebrospinal fluid (0·2 to 0·4 c.c.) from Case I, diluted 1 in 4, was injected intraperitoneally into ten guinea-pigs and five rabbits. Three of the guinea-pigs showed paralytic phenomena a few days later, one became affected seven weeks later, two died of epidemic disease, and four remained well. The rabbits showed transient phenomena, not definitely paralytic, but otherwise the results in them were negative. A little later blood-free cerebrospinal fluid from Case I was injected intraperitoneally into five guinea-pigs with negative results, and 1 c.c. of defibrinated blood into another set of five guinea-pigs, of which one died with paralytic phenomena eighteen days later, and the other four of epidemic disease. Intraperitoneal injections of cerebrospinal fluid from Case II into ten guinea-pigs were without result, while similar injections of 1 c.c. of blood diluted 1 in 3 were followed six or seven weeks later by paralytic phenomena in two out of three animals. Intra-ocular injections of cerebrospinal fluid (0·2 to 0·5 c.c.) from Case II were followed by paralytic phenomena in two out of five rabbits.

These authors also claim to have transmitted the disease through a series of four guinea-pigs and later of two rabbits, using for the first injection material obtained from previously inoculated animals who had developed paralytic phenomena. The exact nature of the material used and the route employed for the injections are not stated.

Control experiments (fifteen rabbits and thirty guinea pigs) were negative.

All the affected animals showed symptoms in from three days to three months after injection (average six to seven weeks); they moved about less, sat hunched up, the hind legs became stiff and weak, and total paralysis preceded death.

Post-mortem examination of the paralysed animals revealed no naked-eye lesions in the internal viscera or nervous system, and at the time of publication the histological examination had not been completed.

Delicate, slender spirochætes, resembling those found in epidemic jaundice, were demonstrated during life and after death in the heart's blood of several of the affected animals, and also in the blood-vessels of the liver.

If we analyse these experiments it will be evident that in the absence of any histological examination of the brain and cord of the affected animals there can be no justification for assuming that the animals had developed disseminated sclerosis. This being so we are justified still less in assuming that the finding of spirochætes in the heart's blood and liver is in any way related to the origin of disseminated sclerosis, whatever may have been its relation to the morbid condition from which the experimental animals were suffering.

(*d*) Simons, using sterile cerebrospinal fluid of a patient with disseminated sclerosis, kept at 0° C. for ten days, inoculated nine rabbits, of which seven remained well. One animal, which had received 3 c.c. in one sciatic region, nine days later developed paralysis of the hind legs and died totally paralysed on the nineteenth day; no naked-eye lesions were found in meninges, brain, or cord. The other animal developed paresis of the hind limbs on the fifth day, which persisted; the animal was killed on the fourteenth day but nothing abnormal was found post mortem.

(*e*) Marinesco inoculated the cerebrospinal fluid of two patients with disseminated sclerosis into six guinea-pigs, of which four were unaffected. The other two, who had received 1 c.c. intracerebrally, presented three or four days later difficulty in moving about. In the fluid obtained by puncture of the fourth ventricle of these animals spirochætes were found similar to those described by Kuhn and Steiner. This fluid injected into guinea-pigs, and a repetition of the experiments *de novo*, all gave negative results.

(*f*) Steiner, in March, 1917, injected 1 c.c. of cerebrospinal fluid from Case I of Kuhn and Steiner's series into an ape (*Macacus rhesus*). The animal remained well until February, 1918, when some awkwardness and weakness of the hind limbs was noticed by the attendant.

This passed off to reappear in June when the limbs were observed to be weak and spastic. The condition persisted and a month later the animal was killed. At the post-mortem examination nothing abnormal was found in the viscera, but focal lesions were visible to the naked-eye scattered irregularly throughout both cerebral hemispheres. Histologically these foci were found to consist of fairly sharply outlined areas characterized by a patchy destruction of medullary sheaths; compound granular cells were present in large numbers, both these and the glia cells containing granules which stained red with scharlach. Proliferation of the glia cells was a prominent feature, and in the periphery of the lesions numerous multi-nucleated glia cells with abundant protoplasm were present, the cells showing a definite tendency to form fibrils. The axis cylinders were relatively intact and there were no vascular changes. The spinal cord apparently was not examined.

Steiner considers that the lesions found are indistinguishable from those of human disseminated sclerosis, but utters a note of warning against drawing hasty conclusions.

(*g*) Rothfeld, Freund, and Hornowski inoculated by a variety of routes guinea-pigs and rabbits with blood and cerebrospinal fluid from four undoubted cases of disseminated sclerosis. The blood of the experimental animals was examined for spirochætes almost daily, minute histological examination was made of the brain and cord, and emulsions of brain and cord from inoculated animals was injected into a further series. In no case were spirochætes found, and the authors express the opinion that the spirochæte found by Kuhn and Steiner was an accidental infection transmitted from animal to animal. Many of the inoculated animals died, but the cause of death in the vast majority of cases was either coccidiosis or tuberculosis. In one animal slight neuroglia changes were found, but precisely similar changes were observed in animals with coccidiosis who had received no injections. In all other respects histological examination of the nervous system was negative. Some of the animals appeared to be ill for a day or two after inoculation with cerebrospinal fluid, the fluid being probably toxic in some way. In no case, however, did the authors succeed in transmitting to guinea-pigs or rabbits any condition resembling human disseminated sclerosis.

(3) *The Finding of Spirochætes in the Brains of Patients dead of Disseminated Sclerosis.*

(*a*) Siemerling was the first to publish a positive result. In the brain of a patient with disseminated sclerosis who died of erysipelas, examined two hours after death, numerous focal lesions were present; minute pieces from the diseased areas were removed and examined by the dark-ground illumination method. In two preparations living spirochætes were found, similar to those discovered by Kuhn and Steiner, but attempts to stain them in sections did not succeed.

(*b*) Büscher reported the finding of spirochætes by the dark-ground illumination method in the brain of a chronic case of disseminated sclerosis; the parasites exhibited undulatory movements from fifteen to thirty-nine hours after death. They could not however be detected in hardened sections of the brain in ordinary silver preparations.

(*c*) Schuster describes the case of a boy which he regards as a combination of juvenile general paralysis and disseminated sclerosis. Mental symptoms were a prominent feature of the illness and in the later stages the pupillary reactions to light became sluggish. At the autopsy the brain was found to be atrophic, the leptomeninges thickened, and the lateral ventricles dilated. The peri-vascular spaces were packed with small lymphocytes and plasma cells, and there were numerous areas of myelin sheath destruction, especially in the cerebral white matter. Spirochætes, hardly distinguishable from the *Spirochæta pallida*, were found in the brain in silver preparations of hardened material. The Wassermann reaction was positive during life in both blood and cerebrospinal fluid and the case appears to us, but not apparently to the author, to be of no decisive importance in relation to the pathogenesis of disseminated sclerosis.

General Discussion and Summary.

In attempting to elucidate the pathology of any obscure disease there is a natural temptation to make comparisons between the disease in question and certain other apparently similar conditions the cause and nature of which are understood. In the case of disseminated sclerosis, however, it is difficult if not impossible to conjure up any analogous condition, nor, even if we could, would such analogy be decisive. In view of the suggested spirochætal origin of the disease one naturally compares it with syphilis of the nervous system, to which it bears certain resemblances in its clinical course and manifestations;

it differs however from syphilis in two important particulars, first by being rigidly confined to the nervous system, and secondly by the irregular, patchy distribution of the essential lesions in marked contrast to such systemic processes as tabes dorsalis and general paralysis.

The past and family histories of our patients, so valuable in the etiological studies of other diseases, tell us nothing as to the origin of disseminated sclerosis. It is neither familial nor epidemic, although its rarity in certain countries (it is said to be unknown in Japan) points rather to some extraneous factor.

The pathogenesis of any disease can be considered from two points of view, first the nature of the morbid process, and secondly its origin. As to the nature of the morbid process underlying disseminated sclerosis two views are held. According to the first or exogenous theory, supported by a majority of observers, the process is set up by some irritant distributed through the nervous system by the blood-stream, and is inflammatory or toxi-infective in character. The second or endogenous theory, advocated particularly by Strümpell and Müller, regards the disease as the result of some developmental or congenital defect of the neuroglia, which is thus rendered more liable to be affected by irritation than is normally the case; in other words the disease is a primary gliosis.

There would appear to be an insuperable obstacle to the acceptance of the second or endogenous theory, namely, the clinical character of the disease, since it is hardly conceivable that a condition so frequently characterized by an acute or subacute onset and a clinical course punctuated at irregular intervals with exacerbations and remissions can be ascribed to a congenital or developmental defect. Müller has attempted to overcome this difficulty first by postulating certain external factors as "agents provocateurs" acting on a neuroglia which is congenitally vulnerable and susceptible, but exactly what these factors are he is unable to say. Secondly, and more important, he attempts to draw a distinction between true disseminated sclerosis and secondary disseminated sclerosis. According to Müller the only true disseminated sclerosis is the chronic progressive case originally described by Charcot, which one can perhaps accept as being clinically intelligible as a primary progressive gliosis, whereas the cases with acute symptoms and a discontinuous clinical course, with which this paper mainly deals, he excludes altogether from the category of true disseminated sclerosis, and regards them as something else which he calls "disseminated encephalo-myelitis."

We have now to inquire whether this differentiation advocated by Müller is warranted by the clinical and histological facts at our disposal. Clinically while it is useful to recognize the chronic progressive and the subacute remittent type of case, the distinction must not be pushed too far, since cases not infrequently occur which are intermediate between the two and serve to link the one type with the other. Secondly there is a definite tendency for the remittent type in its later stages to lose its subacute characters and to take on a chronic progressive course. Thirdly, just as the chronic type of case progresses downhill by an increase in intensity of the same symptoms which initiated the disease, so too one frequently observes in the exacerbations of the remitting type a tendency to the reappearance of symptoms which have already been experienced, so that for example the same arm again becomes astereognostic, the same paræsthesiæ are again complained of in the same part of the body, the same leg again begins to drag, and so on. Fourthly, the localization of the lesions as judged by the symptoms and physical signs is roughly similar in the two types; in both, for example, there is the same curious liability to affection of the optic nerve and tract. Consequently in spite of differences in the chronological order of individual symptoms, the symptomatology of the later stages is very similar in both types, and although the individuality of no disease can be established by its symptomatology alone, this factor nevertheless must be given due weight in an attempt to determine the entity of any morbid condition. Finally, in both types there is the same absence of any obvious etiological factor and the same age incidence.

Histologically no essential differences have been shown to exist between the chronic progressive and the remittent type of case. In the former it is true that a progressive gliosis is perhaps the most prominent feature, and that areas of diffuse gliosis occur apparently unrelated to areas of tissue-destruction. Nevertheless it has been abundantly demonstrated that even in these long-standing cases areas of tissue destruction are present in which the changes are of recent date and associated with an inflammatory reaction. While therefore gliosis may be the predominating feature of the chronic case, it must be recognized that the differences in the histological picture in the two types of cases are differences of degree only; in both types the essential lesions are of the same kind, although variations in the age and intensity of the morbid process undoubtedly occur.

Neither from the clinical nor histological standpoint therefore can we find adequate grounds for distinguishing between *true* and *secondary* disseminated sclerosis as advocated by Müller, and we believe that the two clinical types, namely, the chronic progressive and the subacute remittent, represent variations of the same pathological process. If this conclusion is correct, the endogenous theory automatically becomes untenable, since it is impossible to explain the remittent type with its sudden exacerbations and long remissions on an endogenous basis.

The question therefore arises: Can a disease so variable in its clinical manifestations, and running sometimes a chronic progressive and at others a subacute remittent course, be satisfactorily explained on a single pathogenetic basis? We believe that this is possible provided one assumes the presence of a morbid agent acting with varying degrees of intensity over a considerable period, and since variations in intensity are characteristic of all inflammatory and infective processes, such an assumption is practically equivalent to postulating an inflammatory lesion as the essential morbid process underlying disseminated sclerosis. Arguing on these lines the acute clinical disturbances are to be regarded as the result of an acute inflammatory process, and their partial or complete disappearance represents a dying down of the process with absorption of exudate and consequent functional recovery of the tissues; where however sufficient structural damage has occurred permanent effects will remain. The chronic progressive condition on the other hand, whether it supervenes on a previously more acute phase or whether it has characterized the illness *ab initio*, is evidence of the same morbid process, less intense in its action, but one nevertheless which never becomes entirely inactive. In such cases one expects to meet not so much new focal areas of disease in parts of the brain and cord some distance removed from those already affected, but rather a gradual extension of already existing areas and a consequent spread and intensification of already existing symptoms; in other words, the legs become more paraplegic, an eye more blind.

Again one cannot altogether ignore the existence of cases which after a variable time become definitely non-progressive, and we have already hinted at the possibility of the existence of spontaneous "cures." In the former cases, a small minority of the total, the disease has entirely ceased to be active, while the latter correspond to the "formes frustres" of many other infective processes.

The absence of cytological and chemical changes in the cerebrospinal fluid, as determined by ourselves in common with many other investigators, in no way militates against the hypothesis that the process is an inflammatory one. In the first place it seems probable that the increase in protein and morphological elements when occurring in other conditions should be ascribed to a diffuse or local reaction on the part of the meninges rather than to changes in the nervous parenchyma itself, and meningitic changes although present in some cases cannot be regarded as an invariable feature of the morbid histology of disseminated sclerosis. Secondly, pathological changes in the cerebrospinal fluid may be conspicuous by their absence in such frankly inflammatory conditions as acute poliomyelitis and encephalitis lethargica.

Histological investigations confirm the arguments based on clinical studies. Our own histological examinations have unfortunately been far from complete, but as far as they go they are in agreement with the more recent work which insists on an inflammatory reaction, acute or subacute, in the affected areas. Both Siemerling and Raecke, and Dawson describe a general tissue reaction in the early, and an essentially glia reaction in the later stages, the general architecture of the tissues being to a great extent preserved owing to the relative escape of axis cylinders and ganglion cells. Although the inflammatory phenomena of the earlier stages occupy a more prominent position in the description published by the German writers than in that given by Dawson, the latter nevertheless expresses the opinion that "there is overwhelming evidence that the great majority of the areas have arisen on an inflammatory basis." Both sets of observers lay stress on the fact that in the same individual different stages of the morbid process can be identified in different areas, some of recent origin and others of long standing, a state of affairs entirely in keeping with the clinical histories so characteristic of the remittent type of disseminated sclerosis. Moreover at the edges of areas even where sclerosis is complete there is histological evidence that the morbid process has never become entirely inactive, but is capable either of lighting up acutely, or, and perhaps more frequently, of advancing slowly by peripheral extension. In this connection we hesitate to accept the suggestion put forward by Siemerling and Raecke that the scar tissue formed by the glia proliferation protects the tissues from further damage. On the contrary we consider it much more probable that the virus lies latent in the scar tissue, but capable of initiating further infection when the local or

general conditions permit: in other words we regard the scar tissue as the starting-point from which reinfection originates. Finally both sets of observers agree that the histological changes can only be explained by a variation in the intensity of the morbid process in different areas; thus while rapid destruction of tissue is a feature in some, in others there is little more than a spreading gliosis, which they attribute to the leakage of a diluted virus from the essential primary lesions, and it is on this latter basis that the chronic progressive case finds its readiest explanation.

As regards the origin of the morbid process underlying disseminated sclerosis our own investigations have failed to throw any light on the subject; in no case have we succeeded in transmitting the disease to animals, while our bacteriological and parasitological investigations have been without result. Neither can we admit the claim of those writers, whose work we have reviewed, that they have transmitted the disease to rabbits and guinea-pigs. Even if we admit that in certain instances they have transmitted *a* disease, there is an entire absence of histological proof that the disease so transmitted was disseminated sclerosis. In view however of Steiner's monkey experiment it would seem advisable to continue experimental investigations with *Macacus rhesus*. Neither can we regard the finding of spirochætes in the hepatic vessels and ventricular fluid of inoculated guinea-pigs and rabbits as being of any decisive significance, in the absence of adequate evidence that the animals which harboured the parasite were suffering from disseminated sclerosis. Moreover it is not fully known to what extent spirochætes occur in animals under different conditions of health and disease; they have been found, for example, by one of us (L.S.D.) in the livers of apparently healthy guinea-pigs, while according to Fiessinger they are present in human urine in over 2 per cent. of normal individuals.

Adams in a recent contribution is inclined to support the spirochætal origin of the disease partly on clinical grounds, but mainly owing, first, to the presence in the cerebrospinal fluid of 95 per cent. of his cases of a luetic or paretic reaction to colloidal gold, secondly to the modifications which this reaction undergoes under neo-salvarsan treatment, and thirdly to the beneficial clinical effects of anti-syphilitic treatment in early cases of the disease. We feel however that until the rationale of the colloidal gold reaction is more completely understood, arguments based on the presence and behaviour of the reaction are unsubstantial, while in view of the remissions so characteristic of the disease the

beneficial effects claimed for any therapeutic measures must be treated with the greatest reserve.

Finally the finding of spirochætes in the cerebral hemispheres of two patients dead of disseminated sclerosis needs confirmation and amplification before we should be justified in accepting unreservedly the spirochætal origin of the disease.

While therefore we are of opinion that in spite of recent investigations the origin and nature of the morbid agent has yet to be discovered, we believe that there are sound reasons, both clinical and histological, for the view which regards the morbid process underlying disseminated sclerosis as inflammatory in character.

Conclusions.

(1) It is useful to recognize two clinical types of disseminated sclerosis: (*a*) the remittent type characterized by acute exacerbations at widely varying intervals alternating with quiescent periods, and (*b*) the chronic progressive type.

(2) In the present series (thirty-five patients) the proportion of remittent to chronic progressive cases is as six is to one.

(3) In early cases of the remittent type, once the acute disturbance has subsided, the patient may present no clinical evidence of organic disease over prolonged periods. The possibility of spontaneous cure cannot therefore be entirely denied.

(4) The remittent type in its later stages tends to assume the characteristics of the chronic progressive type.

(5) The great bulk of clinical and histological evidence is opposed to the view that these two types correspond to two different pathological processes. On the contrary, they are to be regarded as manifestations of one and the same disease, namely, disseminated sclerosis.

(6) Cultural and microscopic examination of the cerebrospinal fluid has in our hands thrown no light on the pathogenesis of the disease, and no specific organism has been isolated.

(7) Our attempts to transmit disseminated sclerosis from man to animals (rabbits) have been unsuccessful.

(8) We regard the transmissibility of the disease from man to animals as unproved.

(9) We are of opinion that the evidence in favour of the assumption that the pathogenic agent is a spirochæte is incomplete and in many

respects unsatisfactory, and we consider that the origin and nature of the morbid agent must for the present remain *sub judice*.

(10) We consider that the clinical and histological evidence is overwhelmingly in favour of the view that the morbid process underlying the disease is inflammatory in character.

APPENDIX.

Clinical Notes of Non-Fatal Cases.

Case III.—E. B., girl, aged 18, domestic servant. Admitted to National Hospital, Queen Square, on April 28, 1913.

Family and past history: Only child. Two sisters stillborn. Always delicate.

History of present illness: September, 1912: Retro-ocular pain with rapid failure of vision, so that she could not see her hand held in front of her eyes. October, 1912: Pain disappeared; vision improved so that she could see to get about; noticed difficulty in sitting up in bed unsupported. January, 1913: Tremor of left hand when she used it; could not hold a cup without spilling it; the condition cleared up within three weeks. February, 1913: Sudden weakness of right leg, unable to walk without support since this date; difficulty in holding her water, numerous "accidents"; this lasted for three weeks, and was then replaced by hesitancy of micturition which persists. March, 1913: Paræsthesiæ in right leg; never diplopia, dysarthria, or loss of emotional control.

On examination, April 28, 1913: Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, normal. Vision: acuity, $\frac{1}{60}$, right and left. Both discs are pale all over, somewhat opaque, retinal pigment disturbed, edges clear (primary atrophy with probably a little antecedent œdema). Hearing, normal. Cranial nerves: pupils normal; congenital concomitant strabismus; no diplopia; nystagmus to right > left; weakness right lower face, otherwise negative. Motor.—Head and neck, natural. Upper extremities: no paresis; both arms a little unsteady, left > right: slight sensory ataxia on right; trunk muscles weak: no wasting; umbilical excursion upwards. Lower extremities: considerable weakness and spasticity, right much weaker than left; no wasting or obvious ataxy. Gait: spastic, reeling and very feeble; cannot walk unsupported. Sensory.—Subjective: numbness right leg; girdle sensation. Objective: slight astereognosis and raised threshold to compasses in right hand; diminution of tactile and painful sensibility on right from fifth rib to middle of thigh; some loss of sense of passive position and movement in ankles and toes, right > left; vibration much impaired in lower limbs. Sphincters: hesitancy of micturition. Reflexes: all jerks very brisk, lower > upper limbs; all abdominals absent; both plantars extensor.

Progress: The patient got gradually worse the whole time that she was under observation. July 21, 1913: Numerous paræsthesiæ in all limbs and trunk; both legs very spastic and almost completely paralysed; lower abdominal muscles are also spastic and paralysed; numerous flexor spasms in legs; sensory loss below fourth rib to touch and prick is increasing right > left; intention tremor has developed in both arms, left > right; profound asynergia and dysmetria; well sustained horizontal nystagmus; complete incontinence of urine and fæces; no bed-sores or pyrexia; vision *in statu quo*. December 8, 1913: Complete paraplegia in flexion; sensory loss to all forms below fourth rib is now profound, complete on right, almost so on left; general condition remains fairly good in spite of incontinence.

Summary: Sudden onset, remissions, partial recoveries, then steady and rather rapid progression downhill with few fresh symptoms.

Case IV.—N. C., woman, aged 32, widow. Admitted to National Hospital, Queen Square, on October 31, 1913.

Family history: Father dropped down dead, aged 43, from a ruptured aortic valve. Mother died of pulmonary tuberculosis. Several brothers and sisters alive and well.

Past history: Good. Husband died, aged 29, of rheumatic heart disease. One daughter died of diphtheria: one boy, aged four, alive and well. No miscarriages.

History of present illness: Four years ago sudden attacks of severe rotatory vertigo without deafness or tinnitus; these persisted for two years. Three years ago noticed curious fleeting sensations of numbness in legs and tightness round waist, which have never quite disappeared. Four months ago woke up one morning and found that her left hand was completely paralysed and she had lost all feeling below the left elbow. The right hand was numb and peculiar. She could not tell what she held in her hand unless she looked to see, and her writing became a scribble. She also had a tight band across the stomach and both legs were weak and quite numb; she could not feel hot or cold water in her legs, her walking was very unsteady "as if I was walking on air." The legs have improved, feeling has returned and she can walk better, but cannot even stand unsupported in the dark. The right hand has not altered, but the loss of sensation in the left upper limb gradually extended up to the shoulder, so that the whole arm "has an existence apart from me"; it is not paralysed. No affection of vision, speech, or sphincters.

October 31, 1913: Visceral examination negative; no developmental defects. Vertebral column healthy. Wassermann reaction (blood) negative. Mental condition: normal emotional tone; good type. Vision: acuity, $\frac{6}{12}$ left, $\frac{6}{9}$ right; fields normal; temporal pallor of both discs, left > right. Hearing normal. Cranial nerves: well sustained slow horizontal nystagmus, otherwise normal. Motor: head and neck natural, no rigidity. Upper extremities.—Right: hypotonia distally, no paresis with eyes open; no wasting or trophic changes; all finer movements of fingers characterized by overaction;

fingers wander with eyes shut; sensory ataxy. Left: profound hypotonia and complete inability to apply muscular power with eyes shut; no wasting. Trunk: slight diaphragmatic weakness; nothing else to note. Lower extremities: considerable weakness, left > right; no spasticity; no wasting or obvious ataxy. Gait: weak and ataxic; Rombergism present. Sensory: subjective—paræsthesiæ, limbs and trunk. On examination: complete loss to all forms below shoulder in left upper limb except algometer pressure which is recognized but not localized; loss of sense of passive position and movement is almost complete even at shoulder-joint; slight impairment of cutaneous sensibility in right hand below wrist; partial astereognosis right hand, compass threshold raised, and sense of passive position and movement impaired in wrist and fingers; to the left of the mid-line from the second cervical segment down to the foot there is profound loss to touch, pin-prick and temperature, and a similar condition prevails on the right below the umbilicus; there is profound loss to vibration in left pelvis and lower limb, and a slight impairment in right pelvis and lower limb; the sense of passive posture and movement is normal in the right lower limb, but slightly defective in the left. Sphincters natural. Reflexes: all tendon jerks brisk; all abdominals absent; both plantars indefinite, but probably extensor.

Progress: Two months later the sensory loss over the left arm was not quite so deep, and the patient had some idea of the position of the limb, but the ataxia with eyes shut was still very wild. The loss of deep sensation in both legs had increased and the gait was more ataxic. The right plantar response was definitely extensor, the left indefinite. Otherwise no change.

Summary: This case is regarded as doubtful, seeing that the condition can be explained by an extensive lesion in the upper cervical cord, such as one sees in syringomyelia. On the other hand the previous history of vertiginous attacks, paræsthesiæ, and the presence of temporal pallor points to a dissemination of lesions, and renders the diagnosis of disseminated sclerosis probable, although by no means certain. Attempts to trace this patient have not been successful.

Case V.—N. R., male, aged 32, farmer. Admitted to National Hospital, Queen Square, on November 3, 1913.

Family history: Nothing of importance.

Past history: When aged about 15 he injured the left shoulder (? fracture dislocation); his arm wasted above the elbow and never recovered. In 1904 he contracted a wart-like, venereal sore which was said to be not syphilitic; no evidence of syphilis ever developed.

History of present illness: In 1899 he lost the sense of taste on the left side and his tongue and face felt dead and numb. This disappeared entirely in a few weeks. In 1906 he had a severe attack of furunculosis, and during convalescence he rather suddenly became aware of weakness of the left leg, his gait became unsteady, and he often vomited. His legs then became so weak that he could hardly get about, and he later developed diplopia and urgent micturition with frequent "accidents." After some months he began

to improve, the diplopia disappeared, and his legs recovered sufficiently to allow him to get back to his ranch and do his ordinary work. In 1909 he relapsed and could hardly walk unsupported; he was admitted to Queen Square and was found to have a typical spastic paraplegia, but no other physical signs beyond wasting of the muscles round the left shoulder. During the past four years his condition has varied considerably, there have been no new symptoms beyond weakness of the legs and loss of control over the bladder.

November 3, 1913: Good type and physique. Visceral examination negative: no evidence of syphilis. Wassermann reaction (blood) negative. Mental condition normal. Vision: acuity, $\frac{6}{24}$ right, $\frac{6}{12}$ left; temporal pallor of both discs. Cranial nerves: horizontal nystagmus to right and left, otherwise negative. Motor.—Head and neck normal; upper limbs normal, except for atrophic palsy of muscles round left shoulder and of upper arm, due to old injury; no tremor or ataxia. Lower limbs: severe spastic paraplegia; very little power at any joint, numerous flexor spasms. Sensory.—Subjective: *nil*. Objective: blunting of tactile sensibility in right leg; some loss of sense of passive position and movement in ankles and toes; vibration not tested. Sphincters: retention of urine; requires catheter. Gait: impossible. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Condition unchanged two months later.

Summary: Remittent type in early stages; in later stages assuming a chronic progressive course with absence of new symptoms.

Case VI.—P. E., male, aged 27. Admitted to National Hospital, Queen Square, on August 15, 1913.

Family and past history: Nothing of importance.

History of present illness: Seven years ago he developed diplopia, which persisted for six months. Soon after he had begun to see double he experienced difficulty in holding his water, and walked as if drunk. His walking gradually deteriorated, and he lost all control over his bladder, but after several months both these symptoms improved. The improvement, however, was not maintained, his walking became more unsteady than ever, and his hands began to shake so that he had difficulty in feeding himself. Later his head shook when he talked and his speech became affected. During the past five years he has got gradually worse, but no fresh symptoms have developed. Never paræsthesiæ or vertigo.

On examination, August 15, 1913: Fair type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: Unduly sanguine; defective emotional control. Vision: acuity, $\frac{6}{36}$ right and left (uncorrected); well-marked temporal pallor of both discs. Hearing normal. Cranial nerves: jelly-like nystagmus with eyes at rest; coarse horizontal nystagmus on looking to right and left; weakness of left external rectus and diplopia on looking to left; typical scanning, staccato

speech, very tremulous, with explosive element well marked. Motor: head and neck, nodding tremor when unsupported, greatly accentuated when he talks; upper extremities no paresis, typical intention tremor right and left, dysmetria and asynergia readily demonstrable; trunk normal, can sit up without use of hands; lower extremities, tone increased, slight weakness of dorsi-flexors at ankles, tremulous. Sensory: subjective and objective, nothing to note; vibration not tested. Sphincters: urgent micturition: frequent "accidents." Gait: reeling and drunken, characteristic of cerebellar inco-ordination; steps unequal in size and direction; no Rombergism. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Four months later *in statu quo.*

Note: Chronic progressive type; prominence of cerebellar signs and symptoms.

Case VII.—W. S., male, aged 21. Admitted to National Hospital, Queen Square, on October 31, 1913.

Family and past history: Nothing to note.

History of present illness: Three years ago his arms began to shake when he used them and his speech altered; a little later he walked as if drunk. The general unsteadiness of all four limbs and the affection of speech have since got progressively worse, and he laughs for hours together for no apparent reason. He has been absolutely helpless for twelve months, and more recently has lost control over his bladder. Never ocular disturbance or paræsthesiæ.

On examination, October 31, 1913: Poor type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligence below the average; silly and giggling; laughs when spoken to and at his own tremor. Vision: acuity, $\frac{6}{9}$ right and left; temporal pallor of both discs. Cranial nerves: coarse nystagmus in all directions, no ophthalmoplegia; speech typical of advanced disseminated sclerosis, slow, staccato, explosive, and barely intelligible; some difficulty in swallowing, but never nasal regurgitation. Motor: no obvious paresis or tone changes; even when lying he is a mass of oscillations; tremor of head and limbs of extreme degree greatly accentuated by effort; unable to do anything for himself; dysmetria of upper limbs is well shown. Sensory: subjective and objective negative; vibration not tested. Sphincters: incontinence of urine, feels "call" and passage. Gait: impossible without support, attempts show wild cerebellar inco-ordination. Reflexes: all tendon jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: One month later, *in statu quo.*

Note: Chronic progressive type; profound cerebellar inco-ordination of speech and limbs.

Case VIII.—V. B., male, aged 34, shop-fitter. Admitted to National Hospital, Queen Square, on October 3, 1913.

Family and past history good.

History of present illness: Ten years ago the right arm suddenly became useless: it was not paralysed but he could not control it properly nor distinguish what he held in his hand without looking. In three months the arm was perfectly well again. A little later he became unduly emotional, laughing and crying for no reason; this has got much more obvious lately. A year and a half ago his walking rather rapidly became affected and his friends thought he was drunk (patient is a teetotaller); this symptom has varied considerably. Latterly his left foot has dragged and he tires easily. At the same time he noticed curious sensations of "tightness" and numbness in his face and legs, followed by itching of the thighs; these lasted for six months. Recently he has had aching pain in both legs. Six months ago he experienced difficulty in holding his water; recently he has had difficulty in passing it, and has become impotent. He also noticed an alteration in his speech which became slow and awkward; this defect amuses him and he can always keep up his spirits by talking to himself. Four months ago his hands began to shake; his writing became bad and it took him half an hour to do his collar up. Two months ago his vision got rather poor, but has since improved. Never diplopia or vertigo. During the past eighteen months his condition has varied considerably and at times he seems almost well.

On examination, October 3, 1913: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: very intelligent; grossly defective emotional control; he laughs till he cries. Vision: acuity, $\frac{6}{9}$ partly, right and left; temporal pallor with fluffiness of inner edges of both discs, suggestive of preceding œdema. Cranial nerves: horizontal nystagmus on looking to right and left; no ophthalmoplegia; coarse tremor of tongue; typical dysarthria, staccato, jerky, explosive. Motor.—Head and neck: coarse nodding tremor when sitting and standing; no loss of power in limbs or trunk, no spasticity; well-marked intention tremor especially of arms, right > left: dysmetria and asynergia of both arms. Sensory.—Subjective: pains in legs. Objective: superficial sensation good; some impairment of sense of passive posture and movement in toes and ankles; vibration greatly impaired in pelvis and femora, lost below knees. Sphincters: hesitancy of micturition. Gait: slight dragging of feet: reeling and staggering, well marked disturbance of equilibration; no Rombergism. Reflexes: all tendon jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Two months later *in statu quo.*

Note: Remittent type of ten years' duration; early symptoms separated from later ones by a long interval (eight years). Cerebellar manifestations a prominent feature.

Case IX.—L. K., woman, aged 39, widow. Admitted to National Hospital, Queen Square, on November 25, 1913.

Family and past history negative. Two children, no miscarriages.

History of present illness: Two years ago began to have attacks of severe rotatory vertigo with headache and tinnitus in both ears; these gradually

disappeared and she has had none for over a year. Eighteen months ago she had severe retro-ocular pain and her vision rather rapidly failed, so that three months later she was only able to get about in familiar places. The condition has since remained stationary. One year ago she began to have trouble with the bladder, hesitancy of micturition alternating with precipitancy; occasional "accidents." For the past six months she has noticed curious sensations in arms and legs, "tightness," numbness, "tickling," &c. Never dysarthria, tremor, or disturbance of gait."

On examination, November 25, 1913: Normal appearance. X-ray of sella turcica normal. Sugar tolerance normal. Wassermann reaction (blood) negative. Visceral examination negative. Mental condition normal. Vision: counts fingers correctly at 3 ft., right and left; large scotoma right and left eye, extending into temporal more than into nasal field; both discs very pale—primary optic atrophy. Hearing normal. Cranial nerves: negative; no nystagmus. Motor: normal in every particular. Sensory.—Subjective: numerous paræsthesiæ. Objective: normal; vibration not tested. Sphincters: urgent micturition. Gait: natural. Reflexes: all jerks rather exaggerated; left abdominals normal, right much diminished; both plantar responses flexor.

Progress: One month later *in statu quo.*

Note: Atypical case, but clear evidence of dissemination of lesions. Severe bilateral visual failure.

Case X.—T. R., woman, aged 27, single. Admitted to National Hospital, Queen Square, on November 2, 1913.

Family history: Negative; one of a large family.

Past history: Trivial accident to right knee eighteen months ago, followed by painful swelling of joint.

History of present illness: One year ago the right leg became weak and dragged, and she has not walked about for six months. Weakness of the left leg noticed quite recently. (N.B.—Patient is a very unreliable witness and can give no accurate account of her illness.)

On examination, November 2, 1913: Poor type and physique. Visceral examination and vertebral column normal. Wassermann reaction (blood) negative. Mental condition: poor intelligence; facile, fatuous and inattentive; gross loss of emotional control; laughs at her own disabilities. Vision and hearing normal. Cranial nerves normal; no nystagmus or dysarthria. Motor.—Head and neck: natural. Upper limbs: no loss of power; both hands rather unsteady and tremulous; no very definite ataxia. Trunk: all abdominal muscles spastic and weak. Lower limbs: tone increased; considerable weakness, especially of flexors; numerous flexor involuntary spasms; spastic paraplegia. Sensory.—Subjective: normal. Objective: difficult to test, as examination amuses patient, rendering her an impossible witness; some impairment of both deep and superficial sensation below knees. Sphincters: urgent micturition. Gait: spastic, right leg > left. Reflexes:

all jerks very brisk, especially in lower limbs; all abdominals absent; both plantar responses extensor.

Progress: Two months later unchanged.

Note: Chronic progressive type; lesions not numerous.

Case XI.—F. R., male, aged 28. Admitted to National Hospital, Queen Square, on September 22, 1913.

Family and past history: Negative.

History of present illness: Two years ago his gait became unsteady and his right foot dragged. The condition has varied, but recently has become worse, so that he is unable to walk without support. One year ago he began to have difficulty in voiding his urine, but this has now disappeared. His arms became shaky and weak, especially his right, and he had difficulty in writing. Six months ago the vision in his left eye rather rapidly failed, but has improved recently. During the past three weeks he has been subject to attacks of severe giddiness accompanied by vomiting. Never dysarthria or diplopia; no paræsthesiæ.

On examination, September 22, 1913: Good type, fair physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition natural. Vision: acuity, $\frac{6}{6}$ right, $\frac{6}{24}$ left; no note of ophthalmoscopic examination. Hearing normal. Cranial nerves normal; no nystagmus or dysarthria. Motor.—Head and neck normal. Upper limbs: no spasticity; power below normal, right > left; moderate intention tremor with dysarthria and asynergia, right > left. Trunk normal. Lower limbs: spastic paraplegia in extension; right leg weaker than left; power in both greatly diminished. Sensory: subjective and objective normal; vibration not tested. Sphincters natural. Gait: impossible without support; very spastic. Reflexes: all jerks greatly increased, especially in legs; absent abdominals; both plantar responses extensor.

Progress: Three months later the condition had vastly improved; the intention tremor of the arms had largely disappeared and he could walk unaided. There was less spasticity, and the gait was more reeling and like that seen in cerebellar disease.

Note: Remittent type; onset of different symptoms never very acute.

Case XII.—E. T., woman, aged 35, married. Admitted to National Hospital, Queen Square, on December 11, 1913.

Family history: Nothing to note.

Past history: Has always been "nervous"; two children alive and well; no miscarriages.

History of present illness: Four years ago she complained of pains in the legs, her walking became unsteady, and her hands shook at times. She also became unduly emotional, crying and laughing for no reason, and suffered from urgent micturition with occasional "accidents." She remained in much the same condition for three years, varying round a more or less constant mean. Following a mental shock a year ago her walking became progressively

worse and her hands shook when excited. She now complains of aching pains in hips and arms, and her feet feel stone cold. The emotionalism has almost disappeared. Never ocular symptoms or dysarthria.

On examination, December 11, 1913: Good type, fair physique. Visceral examination, negative. Wassermann reaction (blood), negative. Mental condition, normal; reserved, and good emotional tone. Vision and hearing: normal in every particular. Cranial nerves: nothing to note except ill-sustained nystagmus. Motor.—Head and neck normal. Upper limbs: no loss of power; both hands are rather unsteady and awkward, but there is no true intention tremor or dysmetria. Trunk: very weak; cannot sit up without use of hands; abdominal muscles spastic. Lower limbs: spastic in extension; gross loss of power, left > right; no wasting. Sensory.—Subjective: paræsthesiæ in limbs, especially legs. Objective: slight loss to light touch and pin prick below knees, left > right; definite impairment of sense of position and movement at and below knees, right > left; vibration impaired slightly below eighth thoracic spine, and barely recognized in pelvis and lower extremities, especially on right. Sphincters: urgency of both: feels "call" and passage. Gait: very spastic; can walk a few steps without support; Rombergism present. Reflexes: all jerks exaggerated, lower > upper limbs; all abdominals absent; both plantar responses extensor.

Progress: Condition unchanged two months later.

Note: Chronic progressive type without exacerbations.

Case XIII.—J. B., male, aged 45, shop assistant. Admitted to National Hospital, Queen Square, on December 16, 1913.

Family history negative.

Past history: Always had good health; gonorrhœa twenty years ago; denies syphilis.

History of present illness: Six years ago his right foot began to drag; this got worse for a year and has remained stationary since. Four years ago he rather suddenly lost the use of his left hand; he could move his fingers, but they seemed clumsy, and he could not identify objects in his left trousers pocket. About the same time he had some difficulty in passing his water, which entirely disappeared after a few months. For the past three years he has been unnaturally nervous and apt to burst into tears, "a matter beyond my comprehension." One year ago his left leg began to get weak; his left arm also became rapidly much worse, and he now loses it in bed and it gets "out of control." Also, "When I move my right hand up to my mouth, the left arm goes across and catches hold of it." His left arm often feels numb and his feet cold. He has never noticed any loss of sensation in arms or legs. No defect of speech or vision, and no tremor.

On examination, December 16, 1913: Good type and physique, rather stout. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition normal; no loss of emotional control detected. Cranial nerves normal; no ophthalmoplegia or nystagmus. Vision and hearing

perfect. Motor.—Head and neck: no tremor, rigidity or wasting. Upper limbs: power at shoulder and elbow is impaired on left, but there is no sign of wasting and the electrical reactions are normal; power in hand is normal, there is a profound degree of sensory ataxia in the left arm and tabetic athetosis; in the right arm power is normal, except for flexors of wrists and fingers, which are definitely weak and wasted with lowered faradic excitability; no ataxia or tremor. Trunk good. Lower limbs: both spastic and weak, right much more so than left; flexors weaker than extensors; no wasting. Vertebral column normal. Sensory.—Subjective: occasional tingling in both hands. Objective: complete loss to light touch over left cervical segments 2 to 5 and slight impairment over left C. 6 and 7, and right C. 2 to 5; pin-prick and temperature lost or impaired over C. 2 to 7 on left, and C. 2 to 6 on right; profound loss of sense of passive position movement whole of left arm, complete in hand; no threshold for compasses in left hand, which is completely astereognostic; threshold to compasses in right hand = 2·5 cm.; no astereognosis; vibration lost in left upper limb, good in right; completely lost in spinal column below sixth spine, and impaired in left pelvis and lower limb. Sphincters natural. Gait: spastic, right leg > left; no ataxy or Rombergism. Reflexes: triceps jerks brisk, right and left; biceps and supinator present and normal on right, absent on left; all abdominals absent; both plantar responses extensor; associated movements are present in the upper limbs—e.g., grasping with right hand is associated with a similar movement in left.

Progress: No change three months later.

Note: This must be regarded as a very doubtful case. The patient insisted on his loss of emotional control, but it was not demonstrable during the time that he was under observation. The rest of the condition can be explained by a central lesion of the upper cervical cord such as occurs in syringomyelia; at the same time neither the clinical course nor physical signs can be regarded as typical of syringomyelia.

Case XIV.—M. B., woman, aged 31, married. Admitted to St. Thomas's Hospital on January 3, 1914.

Family history negative.

Past history: Chlorosis at age of 15. Three children alive and well; one twin stillborn (difficult labour); no miscarriages.

History of present illness: Eleven years ago she noticed pains and various odd sensations in her limbs, especially the left arm and leg, and simultaneously her walking became unsteady. A year later she became subject to sudden attacks of rotatory vertigo, in which she invariably fell to the left, accompanied by headache and noises in the ears; she has had none of these attacks during the past two years. Ten years ago she began to have difficulty in holding her water; this has gradually increased, and she now has frequent "accidents." Eight years ago the paræsthesiæ and difficulty in walking almost entirely disappeared, but after nine or ten months her walking rapidly got bad again, so that her friends thought she was drunk. At the same time she

became unduly emotional and "laughed at everything." These various symptoms have persisted, but vary enormously in their intensity from time to time, the improvements sometimes lasting for several months. On the whole, however, her legs have got weaker, and for six months she has been unable to walk at all. Six months ago her left hand began to shake, and she had difficulty in using a fork. Two months ago she was told that her speech was "funny," but she never noticed any alteration herself. Three weeks ago she woke up with a squint, and has seen double ever since.

On examination, January 3, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: very intelligent; defective emotional control. Vision: acuity, $\frac{6}{12}$ right, $\frac{6}{9}$ left; both discs pale all over and clear cut. Hearing normal. Cranial nerves: weakness right external rectus with internal strabismus; fine nystagmus of moderate speed with both lateral and vertical movements; no dysarthria. Motor.—Head and neck normal. Upper limbs: right normal; slight weakness of hemiplegic type on left, with intention tremor and dysmetria. Trunk normal. Lower limbs: spastic paraplegia in extension; flexors much weaker than extensors and left much weaker than right. Sensory.—Subjective: numerous paræsthesiæ. Objective: only loss discovered is to vibration, which is lost or impaired in pelvis and lower limbs; left > right. Sphincters: urgent micturition; feels "call" and passage. Gait: spastic and ataxic; well marked disequilibration and asynergia; no Rombergism. Reflexes: all tendon jerks much exaggerated: abdominals absent; both plantar responses extensor.

Progress: Six weeks later the gait was much improved and she could walk a few steps unaided.

Note: Remittent type with exacerbations and wide dissemination of lesions.

Case XV.—H. S., woman, aged 25. Admitted to St. Thomas's Hospital on January 1, 1914.

Family history negative.

Past history: Asthma up to the age of 16.

History of present illness: Eighteen months ago woke up to find that she saw double, and that she could not shut the right eye, which was turned outwards. In six months time she was quite well again. Six months ago her walking rather rapidly became unsteady, and she reeled about as if drunk. One month ago her walking became much worse, the diplopia recurred, and the left arm suddenly became useless, so that she could not control it or feel what she held in her hand. She also noticed numbness of the right leg and aching pain in the right arm and left leg. Never dysarthria or sphincter disturbance.

On examination, January 1, 1914: Good type, poor physique. Visceral examination: congenital pulmonary stenosis; no cyanosis; otherwise negative. Wassermann reaction (blood) negative. Mental condition: intelligent;

poor emotional tone; unduly sanguine. Vision: acuity, $\frac{6}{24}$ (corrected), right and left; central scotoma for colour in both eyes; discs distinctly pale, especially in temporal halves. Hearing: normal. Cranial nerves: weakness of right internal rectus; rapid nystagmus on looking to the right, otherwise negative; no dysarthria. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: good power; no intention tremor; profound sensory ataxia on left with tabetic athetosis. Trunk normal. Lower limbs: slight spasticity with some weakness of flexors. Sensory.—Subjective: paræsthesiæ in limbs. Objective: superficial sensation perfect: profound loss of sense of passive position and movement in left arm, complete in fingers; complete astereognosis, no threshold obtainable to compasses; vibration not tested. Sphincters natural. Gait: no obvious spasticity, but profound cerebellar inco-ordination; no Rombergism; cannot walk without support. Reflexes: all jerks increased; all abdominals absent; both plantar responses extensor.

Progress: Ten weeks later the walking had improved, but was still very inco-ordinated. Otherwise *in statu quo.*

Note: Typical remittent type with wide dissemination of lesions.

Case XVI.—E. M., woman, aged 25, married. Admitted to National Hospital, Queen Square, on October 23, 1913.

Family history: Mother died of "creeping paralysis," aged 47.

Past history: Good. Three healthy children, no miscarriages.

History of present illness: Six years ago, three months after a normal confinement, her walking became unsteady, her left hand weak, and she had difficulty in passing her water. Nine months later all these symptoms became greatly aggravated, micturition became urgent, she developed diplopia, her sight began to fail, she lost control over her emotions, and had frequent boring pains in the legs. At this time she was admitted to the National Hospital, when the note was as follows: Visual acuity, $\frac{6}{24}$ right and left, temporal pallor, nystagmus, intention tremor of arms, spastic paraplegia, with increased tendon reflexes, absent abdominals, and double extensor plantar responses. She rapidly improved, the diplopia disappeared, and except for some slight unsteadiness on her legs she remained quite well for four years. Two years ago, three months after her third confinement, her walking rapidly deteriorated again, and she can now only get about the house by holding on to things. Six months ago micturition again became urgent, but there have been no "accidents." Two months ago she suddenly experienced difficulty in getting her words out and her head began to shake when she talked. Her right hand had also become shaky; and her legs go quite numb from the knees downwards.

On examination, October 23, 1913: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: rather sanguine; no loss of emotional control. Vision: acuity, $\frac{6}{12}$ right, $\frac{6}{24}$ left: right disc generally greyish but whiter in temporal half, edges

clear; left disc very white and atrophic looking. Hearing normal. Cranial nerves: no ophthalmoplegia; jelly-like nystagmus with eyes at rest: quick nystagmus of wide amplitude on looking in all directions. Articulation slow, scanning, syllabic, and explosive; slight tremor of tongue. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: no weakness; intention tremor of moderate degree in both arms; well-marked dysmetria, right and left. Trunk: rather weak; no local palsy. Lower limbs: both a little spastic, considerable weakness, right > left, especially of flexors, and well marked intention tremor. Sensory.—Subjective: paræsthesiæ in legs. Objective: no disturbance except slight impairment of sense of position in ankles and toes; vibration not tested. Sphincters: urgent micturition. Gait: only possible with support; generalized tremor, reeling and drunken, slight spasticity; no Rombergism. Reflexes: all jerks greatly increased; all abdominals absent; both plantar responses extensor.

Progress: Unchanged two months later.

Note: Typical remittent case; onset and exacerbation related to confinement. Generalized cerebellar ataxia.

Case XVII.—L. E., woman, aged 34. Admitted to St. Thomas's Hospital on February 12, 1914.

Family history negative.

Past history: Rheumatic fever, aged 15. Always been "hysterical."

History of present illness: Two years ago her left arm and leg suddenly became weak; recovery within a week. Two months later she noticed that she was blind in the left eye, and began to experience tightness and tingling in the right arm and hand, which has persisted. Six months ago her walking became unsteady, especially in the dark. No dysarthria, diplopia, or sphincter trouble.

On examination, February 12, 1914: Poor type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: highly suggestible; good emotional tone. Vision: acuity, $\frac{6}{24}$ left, $\frac{6}{9}$ partly right; concentric limitation of visual fields; left disc pale all over, edges clear; right disc slight temporal pallor. Hearing normal. Cranial nerves negative, no nystagmus. Motor: No paresis or intention tremor; definite sensory ataxia of right arm with well-marked tabetic athetosis. Sensory: various disturbances of cutaneous sensation can be manufactured or dispersed by suggestion; compasses threshold 1·0 cm. left palm, 3·0 to 3·5 cm. right palm: astereognosis right hand and disturbance of sense of passive posture and movement; questionable impairment of deep sensation in right leg; vibration not tested. Sphincters natural. Gait: slight tabetic ataxia of right leg; Rombergism present. Reflexes: all tendon jerks increased, right > left; all abdominals absent: right plantar response extensor, left flexor.

Progress: The patient was readmitted three months later with an hysterical gait, which disappeared under treatment.

Note: Remittent type with superadded hysterical manifestations.

Case XVIII.—E. C., woman, aged 33. Admitted to National Hospital, Queen Square, on February 19, 1914.

Family and past history: Good. Mild influenza two months ago.

History of present illness: Three weeks ago the left hand suddenly "went funny and useless" so that she could not feel things properly, followed two days later by weakness of the left leg and urgent micturition. She had a severe headache which persisted for four days, and then gradually disappeared. No vomiting, vertigo, or diplopia. The left hand now feels numb and cold.

On examination, February 19, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing normal. Cranial nerves: no nystagmus; definite weakness of right lower face with emotional movements only; otherwise negative. Motor.—Head and neck normal. Upper limbs: right normal; no paresis of left arm except when eyes are closed or limb is screened from view during testing; tabetic athetosis of left hand with pronounced sensory ataxy of whole limb. Trunk normal. Lower limbs: extended and adducted with some extensor rigidity, left much > right; some weakness especially of flexors on left, power good on right. Sensory: slight impairment to touch and pinprick below left elbow; partial astereognosis of left hand, compass threshold 4·5 cm. left palm; impaired sense of passive posture and movement whole of left upper limb, more marked distally; vibration not tested. Sphincters: urgent micturition. Gait: spastic, left much greater than right; no gross inco-ordination; Rombergism negative. Reflexes: all tendon jerks exaggerated, left > right; abdominals diminished on left, normal on right; both plantar responses extensor.

Progress: The patient rapidly improved. One month later the right plantar response was flexor, sphincter control was normal, and the loss of deep sensibility in the left arm was much less.

Note: Early case; acute onset with lesions in spinal cord and subthalamic region, and rapid improvement.

Case XIX.—F. G., woman, aged 23. Admitted to St. Thomas's Hospital on June 8, 1914.

Family history good.

Past history: Always high spirited. Six years ago had "St. Vitus's dance," and "could not control right arm"; well in six weeks. Otherwise good.

History of present illness: One month ago she experienced pains in both hands and forearms, especially the left, with numbness and loss of feeling. This got worse for four days until the hands were "useless"; they were not paralysed, but she could not feel what she held in her hands and dropped objects without being aware of it. The numbness has now spread up beyond the left elbow. At the same time her legs felt numb, and she felt as if a belt were tied round her chest; both these symptoms rapidly disappeared. One week ago she had a sensation as if someone were pouring water down her

neck and it was trickling down her left side, and she began to have difficulty in holding her water, but has had no "accidents." No other symptoms; walking entirely unaffected.

On examination, June 8, 1914: Good type; physique much above average. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing normal; first-rate witness. Cranial nerves: no ophthalmoplegia; slow nystagmus of moderate amplitude on conjugate deviation to the right; otherwise negative. Motor: Head and neck normal. Upper limbs: there is no gross paresis, but on the left there is a slight but appreciable weakness of the biceps and flexors of wrist and fingers; tested with the eyes shut there is an apparent weakness of all muscles; no wasting or tremor; the movements of both hands, the left more than the right, are extremely awkward and suggestive of spasm, yet on manipulation no spasm is present; there is well-marked sensory ataxia (left > right) with loss of direction, and with the arms outstretched and eyes closed the fingers and hands wander into all kinds of grotesque positions of which the patient is unconscious; writing is only possible with the eyes open. Trunk and lower limbs: normal in every particular. Sensory.—Subjective: numbness of both hands. Objective: slight impairment of tactile sensibility in left arm and hand, corresponding roughly to C. 5 and 6 segments; prick, temperature and localization perfect; profound loss to compasses both hands, threshold 5 cm. right, 7·5 cm. left; vibration slightly diminished left hand and carpus, normal elsewhere; passive position and movement—profound loss distally in both upper limbs (left > right), good at shoulders; complete loss to size, shape, weight and consistence in left hand, and almost complete loss in right. No disturbance in trunk or lower extremities. Sphincters: precipitate micturition. Gait normal. Reflexes: all tendon reflexes active except left biceps jerk which is absent; abdominals present and equal, both plantar responses flexor.

Progress: Three weeks later the left biceps jerk had returned, sphincter control was normal, there was no appreciable disturbance of deep sensation in the right hand, and that in the left was much less intense. Nystagmus was still present. Six months later (January, 1915) the patient felt perfectly well, and the only physical sign was nystagmus on looking to the right. In January, 1920, the patient was seen again; she had remained in perfect health, was married with two healthy children, and there was no physical sign of organic disease.

Note: Sudden onset with symptoms pointing to lesion of posterior columns in upper cervical region. Rapid recovery and disappearance of all physical signs; in perfect health six years later.

Case XX.—R. I., girl, aged 19. Admitted to St. Thomas's Hospital on June 2, 1914.

Family history: Twin sister excitable and emotional.

Past history: Excellent.

History of present illness: One year ago she was noticed to be unduly irritable and peevish, and complained of her legs feeling tired; shortly afterwards her walking become unsteady and she fell down if she attempted to run. Ever since she has staggered as if drunk and now can barely walk without support. At the same time she began to have attacks of uncontrollable giggling and laughing, and had difficulty in holding her water, with numerous "accidents." She also complained of curious sensations in her legs, which felt numb and "too full." Her hands also became unsteady, especially the left, so that she could not play the piano and her writing deteriorated. No alteration of speech, but her singing master noticed that her singing voice was shaky. No ocular symptoms or vertigo. The condition has slowly got worse, but no fresh symptoms have appeared.

On examination, June 2, 1914: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligent and observant; very sanguine and indifferent as regards her disabilities; defective emotional control. Vision and hearing, normal. Cranial nerves: inconstant nystagmus on conjugate deviation, slow jerks on looking to the right, rapid to the left; otherwise negative; no dysarthria. Motor.—Head and neck, normal. Upper limbs: no loss of power; moderate intention tremor, left much > right, with asynergia and dysmetria. Trunk: No weakness; combined flexion of hip and trunk well shown. Lower limbs: adducted and extended; considerable extensor spasm; weakness left > right, mainly of flexors at all joints and abductors at hip-joints; intention tremor present. Sensory.—Subjective: numbness of legs. Objective: cutaneous sensibility perfect; impairment to compasses and passive position and movement left lower limb; complete loss to vibration in lower limbs, profound loss in pelvis and lumbo-sacral spine, impaired in lower thoracic spine. Sphincters: urgent micturition. Gait: slighly spastic, left > right; Rombergism doubtful; general disequilibration, tottering and staggering; no synergic movement of arms; cannot bend back without losing balance. Reflexes: tendon jerks in arms exaggerated, in legs multiple; all abdominals absent; both plantar responses extensor.

Progress: Two months later impairment of deep sensation in lower limbs had increased, Rombergism was definitely present, and walking was impossible without support. Nystagmus was constantly present.

Note: Chronic progressive type with wide diffusion of lesions in brain, brain-stem and cord.

Case XXI.—I. W., woman, aged 25. Admitted to St. Thomas's Hospital on August 27, 1914.

Family and past history good.

History of present illness: Six years ago she suddenly became blind in the left eye; after a week the sight rapidly returned. Just over a year ago she had a "nervous breakdown," the chief symptoms being severe aching pains in the legs and back, lassitude and emotional instability; she has never been well since. Five months ago she was drenched in a thunderstorm and caught a

chill; her legs felt numb and painful and she had pins and needles in her fingers. After a few days in bed she got up to find that her walking was unsteady, and this has got worse; she reels about like a drunken person and is at times unable to walk without assistance. Quite recently she has had attacks of rotatory vertigo. No diplopia, dysarthria, or sphincter trouble.

On examination, August 27, 1914: Good type and physique. Visceral examination, negative. Wassermann reaction (blood) negative. Mental condition: unduly optimistic and sanguine; defective emotional control. Vision and hearing normal; visual acuity is $\frac{6}{6}$ in both eyes, and both optic discs are of good colour. Cranial nerves: nystagmus on lateral movements, slow to the left, rapid to the right; otherwise negative. Motor.—Head and neck: nodding tremor when unsupported. Upper limbs: no paresis; fine static tremor. Trunk: good. Lower limbs: no definite paresis; slight extensor spasticity. Sensory.—Subjective: paræsthesiæ in limbs, legs > arms. Objective, normal. Sphincters natural. Gait: very ataxic, reels about; profound asynergia, typical of cerebellar disease; no Rombergism. Reflexes: All jerks very brisk; all abdominals absent; both plantar responses extensor.

Progress: No change two months later. Six months later patient was reported to have developed difficulty in talking and severe tremor of both arms, but these findings have not been included in the statistical table.

Note: Remittent type; no objective evidence of optic nerve lesion in spite of history of sudden amaurosis six years previously.

Case XXII.—G. R., male, aged 22. Admitted to St. Thomas's Hospital, January 19, 1915.

Family and past history, good.

History of present illness: Five years ago his speech began to drawl and he experienced tight feelings round his knees. Later he began "to get shaky all over," especially when excited, and he "got in a tangle with his words." His walking became unsteady as if he were drunk. In July, 1911, he was admitted to St. Thomas's Hospital, when the following note was made: Scanning speech, nystagmus, slight intention tremor of arms, cerebellar gait, exaggerated reflexes, double extensor plantar response. On discharge two months later he had much improved. He remained fairly well for three years, experienced no more paræsthesiæ, and his walking at times seemed almost normal. Some months ago he noticed the vision of his left eye to be failing, and six weeks ago all his symptoms gradually got much worse again. He became very emotional and excitable, his speech at times was barely intelligible, and his walking more unsteady than ever. He also got very sleepy and seemed unnaturally hungry. No vertigo, diplopia, or sphincter trouble.

On examination, January 19, 1915: Good type and physique. Visceral examination, negative. Wassermann reaction (blood) negative. Mental condition: excitable; laughs at his own tremor. Vision: acuity, $\frac{6}{18}$ left, $\frac{6}{9}$ right; scotoma to colours in left eye in nasal field, not quite reaching fixation point; temporal pallor of both discs, left > right. Hearing, normal. Cranial

nerves: horizontal nystagmus; weakness of right lower face, especially with emotional movements. Typical dysmetria, slow syllabic, tremulous, monotonous, with overaction. Motor.—Head and neck: to-and-fro tremor, accentuated when he talks. Upper limbs: no paresis; slight intention tremor, especially with rapid movements; dysmetria and dysdiadokokinesis well marked; breaks pencil when writing. Trunk: combined flexion of hip and trunk; some tremor in sitting position. Lower limbs: no paresis; tremulous and awkward. Sensory: subjective and objective, normal. Sphincters, natural. Gait: staggering and reeling; gross asynergia; no Rombergism. Reflexes: all tendon jerks exaggerated; abdominals brisk and equal; right plantar response extensor, left indefinite.

Progress: Unchanged four weeks later.

Note: Remittent type with little tendency for development of fresh lesions. Cerebellar inco-ordination a prominent feature.

Case XXIII.—E. C., woman, aged 27, nurse. Admitted to St. Thomas's Hospital on February 1, 1915.

Family history: Father paralysed in legs for thirty years.

Past history good.

History of present illness: Seven months ago suddenly developed diplopia, which persisted for four days. A month later she suddenly lost the use of her left leg and fell down in the street; the leg seemed absolutely numb. Two weeks later the power and sensation began to return, and in another two weeks her walking was almost normal again. About this time she began to notice curious sensations in both legs and round her waist, "tight feelings," cramps, tinglings, &c. Three months ago she experienced urgency of micturition and the left leg again suddenly became weak. No tremor, dysarthria, or vertigo.

On examination, February 1, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition normal; first-class witness. Vision and hearing normal, except for a very doubtful temporal pallor of both discs. Cranial nerves: slow nystagmus on looking to left, otherwise negative. Motor.—Head and neck, trunk and limbs, normal. Lower limbs: slight extensor spasticity with weakness of flexors on left, power good on right, no ataxia. Sensory.—Subjective, paræsthesiæ. Objective: normal in every particular. Sphincters: slight urgency of micturition. Gait: weak and spastic, no Rombergism. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress: Two months later both legs were more spastic and weaker.

Note: Early case; remissions after acute exacerbations.

Case XXIV.—H. W., man, aged 26, soldier. Admitted to St. Thomas's Hospital on February 3, 1915.

Family and past history good.

History of present illness: Ten weeks ago patient had a seizure and was

unconscious for an hour; on regaining consciousness he complained of severe headache and retro-ocular pain. A few days later he noticed that he was nearly blind in his right eye. He remained in bed for a month owing to severe giddiness every time he moved, accompanied by vomiting. He also had difficulty in holding his water and had to answer the call the moment he felt it. Four weeks ago he noticed that his hands were unsteady, and he also had cramp-like pains in his legs. His general condition has recently improved.

On examination, February 3, 1915: Fair type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: intelligent; unduly sanguine and distinctly emotional. Vision: acuity, $\frac{3}{60}$ right, $\frac{6}{6}$ left; field in right eye is greatly contracted and there is no colour vision; there is a central scotoma involving the fixation point, spreading out into the temporal field more than the nasal; the field in the left eye is normal; the right disc is pale all over, the edges are slightly blurred, but there is no measurable swelling; the left is normal. Hearing normal; no vertigo now. Cranial nerves: except that the right pupil reacts rather sluggishly to direct light the pupillary reactions are normal; weakness of right external rectus; rotatory nystagmus on lateral movements, especially to the right; otherwise negative. Motor.—Head and neck, nodding tremor, when unsupported. Trunk and limbs: no paresis, hands are a little unsteady, but there is no true intention tremor or inco-ordination; writing is good. Sensory: no objective impairment. Sphincters: urgent micturition. Gait natural. Reflexes: all tendon jerks exaggerated; abdominals present and equal; both plantar responses flexor.

Progress: A month later vision was unchanged. He feels depressed, but laughs when spoken to. Urgency of micturition has increased with several "accidents." Numerous fleeting paræsthesiæ, especially in arms. Gait a little uncertain, but not definitely cerebellar.

Note: Early case; acute onset with loss of consciousness; wide dissemination of lesions.

Case XXV.—C. W., woman, aged 37, married. Admitted to National Hospital, Queen Square, on February 15, 1915.

Family history: Mother is "nervous."

Past history: Always of a nervous disposition.

History of present illness: When pregnant fifteen years ago she noticed that her legs frequently twitched; this has persisted, and she has never been able to walk fast since, although not regarding this as a disability. Ten years ago her left eye rapidly became nearly blind; after a few weeks the sight returned, and she believes it is now quite good. Four years ago she had three severe attacks of rotatory vertigo, associated with vomiting and headache. Three weeks ago, after a thorough wetting, she had severe tingling followed by coldness and numbness extending up the legs to the waist; she also felt as if a tight band were round her waist. These sensations have gradually diminished. Recently she has had slight frequency of micturition, but no urgency.

On examination, February 15, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition, vision, and hearing normal; visual acuity is full in both eyes and there is no pallor of the discs. Cranial nerves negative. Motor.—Head, neck, and upper limbs normal. Trunk: weakness of muscles below umbilicus. Lower limbs: slight extensor spasticity and weakness of flexors. Sensory.—Subjective: numbness from waist downwards. Objective: no definite impairment; vibration not tested. Sphincters: natural. Gait: spastic. Reflexes: arm jerks brisk; leg jerks greatly exaggerated; upper abdominal reflexes present, lower absent; both plantar responses extensor.

Progress: Six weeks later the gait had greatly improved, and the numbness had almost disappeared.

Note: Remittent type extending over a long period; very little actual disability.

Case XXVI.—R. T., man, aged 29, porter. Admitted to St. Thomas's Hospital, April 23, 1915.

Family history negative.

Past history: Typhoid fever, aged 25.

History of present illness: Nine months ago he began to see double; this has persisted. Five months ago, when out walking, he suddenly became unsteady on his legs and nearly fell down; he had considerable difficulty in getting home. The same evening his left hand began to shake so that he could hardly feed himself. Since then his walking and tremulousness have got worse, and his head shakes when he moves about. During the past month he has been subject to sudden attacks of rotatory vertigo without tinnitus or vomiting, in which he tends to fall to the left. Never dysarthria, paræsthesiæ, or sphincter trouble.

On examination, April 23, 1915: Fair type, good physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: no loss of emotional control, but undue optimism and indifference to his disabilities. Vision: acuity, right uncorrected $\frac{6}{60}$, corrected $\frac{6}{12}$; left $\frac{6}{9}$; fundi normal, except for myopia in right eye. Hearing good. Cranial nerves: pupils normal; slight ptosis on right, and weakness of right external and internal recti with diplopia; coarse slow nystagmus in all directions; otherwise negative; no dysarthria. Motor.—Head and neck: nodding tremor of head, increased by excitement and when he walks. Upper limbs: no paresis; well marked intention tremor, left > right, with dysmetria and dysdiadokokinesis; all movements clumsy and laboriously slow; no sensory ataxia. Trunk: combined flexion of hip and trunk well shown. Lower limbs: a little extensor spasticity; no paresis; intention tremor, left > right. Sensory.—Subjective: normal. Objective: slight astereognosis in right hand, with lowering of compass threshold (2·5 cm.); no definite loss of passive posture and movement; otherwise negative; vibration normal. Sphincters natural. Gait: tremulous, unsteady and reeling; well marked asynergia;

Rombergism negative. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress: Three months later his walking had enormously improved and his hands were much steadier.

Note: Early case; remittent type; cerebellar manifestations prominent.

Case XXVII.—M. F., woman, aged 21, servant. Admitted to St. Thomas's Hospital on May 19, 1915.

Family history: Both parents, two brothers and one sister all died of phthisis.

Past history good.

History of present illness: Eight years ago her right hand suddenly became useless; she could not grasp things properly nor feel what she held in her hand. Ten days later the right leg was affected and she stumbled when walking. This was shortly followed by the appearance of tremors in the arms, especially the right, which rendered dressing and feeding very difficult. Her speech also was said to have altered. In ten months all symptoms had entirely disappeared and she felt perfectly well. Four years ago she had precisely similar symptoms, though not nearly so severe; after four months she again got quite well. One year ago she noticed curious sensations in the right arm and leg, which began to shake when she moved them; she could not identify objects in the right hand, and her speech became slow and stammering. She improved for a time, but six months ago got much worse and has gone downhill ever since. Her gait has become unsteady, she has difficulty in passing her water, and has become very emotional and unable to control her feelings. Recently she has had attacks of vertigo. No ocular symptoms.

On examination, May 19, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition intelligent; profoundly emotional and laughs inordinately at her own tremor. Vision: acuity normal; no ophthalmoscopic examination. Hearing good. Cranial nerves: fine nystagmus on lateral movements: typical ataxic dysarthria, slurring, staccato, monotonous, breathless. Motor.—Head and neck: well-marked nodding tremor. Upper limbs: no paresis; well-marked intention tremor and asynergia, right > left; tabetic athetosis of right hand. Trunk: combined flexion of hip and trunk well marked. Lower limbs: no paresis or definite hypertonia; intention tremor, right > left. Sensory.—Subjective: numerous paræsthesiæ. Objective: definite impairment of sense of position and movement in right hand with raised threshold to compasses (3·5 cm.) and partial astereognosis; otherwise normal. Sphincters: hesitancy of micturition. Gait: no spasticity; tremulous, reeling, and staggering: profound asynergia; no Rombergism. Reflexes: all tendon jerks exaggerated: all abdominals absent; right plantar response flexor, left extensor.

Progress: No change four weeks later.

Note: Remittent type; cerebellar manifestations prominent.

Case XXVIII.—M. S., woman, aged 30, married. Admitted to St. Thomas's Hospital on June 14, 1915.

Family history good.

Past history: Always of a nervous disposition.

History of present illness: Nine years ago she had an illness diagnosed as chorea, during which "her right arm shook whenever she used it"; in three months' time she was quite well again. Three years ago she noticed that she frequently laughed and cried for quite inadequate reasons. At about the same time her walking became unsteady, as if she were drunk, and she had difficulty in holding her water, with frequent "accidents." After about twelve months these symptoms disappeared, but eight months ago they reappeared in a somewhat exaggerated form, together with a coarse tremor of the right arm, so that she had difficulty in writing and in feeding herself. Recently she has had attacks of rotatory vertigo without tinnitus, and the unsteadiness of gait, emotionalism, and loss of control over the bladder have become more pronounced. Never ocular symptoms, dysarthria, or paræsthesiæ.

On examination, June 14 1915: Good type, fair physique. Visceral examination: slight visceroptosis; otherwise negative. Wassermann reaction (blood) negative. Mental condition: intelligent; very sanguine and facile; laughs at her own tremor; "my expression does not reflect my feelings." Vision: acuity, right $\frac{6}{12}$, left $\frac{6}{6}$ partly; fields not tested; whole of right disc pale compared with left, especially in temporal half; left disc physiological. Hearing normal. Cranial nerves: no ophthalmoplegia; coarse nystagmus with lateral movements; no dysarthria. Motor.—Head and neck: to-and-fro tremor when unsupported. Upper limbs: slight weakness on right compared with left; no spasticity; typical intention tremor, right much > left; asynergia and dysdiadokokinesis, right > left. Writing shows pronounced dysmetria. Trunk: combined flexion of hip and trunk present. Lower limbs: slight extensor spasticity on right, with slight weakness of flexors; no definite paresis on left; no tremor. Sensory: subjective and objective, normal in every particular. Sphincters: precipitate micturition; frequent "accidents." Gait: can just walk without help; not obviously spastic, but reeling, titubating and very unsteady; no Rombergism. Reflexes: all tendon jerks greatly exaggerated, right > left; all abdominals absent; both plantar responses extensor.

Progress: Two months later she could walk round the ward without assistance, but was otherwise *in statu quo.*

Note: Remittent type tending to chronic progression in later stages; no sensory disturbances in spite of wide dissemination of lesions.

Case XXIX.—F. O'B., woman, aged 48, dressmaker. Admitted to St. Thomas's Hospital on June 16, 1915.

Family history: One of ten children; first three were stillborn, all others alive and well except patient and a younger sister, who is undeveloped both physically and mentally.

Past history: Always "suffering with her nerves"; neurasthenia twelve years ago with numerous phobiæ and apprehensions.

History of present illness: Ten years ago her "nerves" were bad, the sight of the left eye was affected and she had difficulty in holding her water. She improved after a few months, and remained fairly well for nearly three years. Seven years ago her left arm suddenly became useless; it was not paralysed, but she dropped things without knowing it and could not feel properly; her gait became affected shortly after and she walked as if drunk. In six months time she had completely recovered, but a little later her right arm became weak, she developed a squint in the left eye and saw double, she had frequent attacks of vertigo, her right leg dragged, and she lost control over her bladder. The diplopia and vertigo disappeared after a year, and although her walking improved, the other symptoms have more or less persisted, but her condition has varied a great deal from time to time. One year ago she had a "nervous breakdown," became unduly emotional, and lost control over the rectum. Six weeks ago she suddenly lost the use of both legs completely and has been in bed ever since. No dysarthria or intention tremor.

On examination, June 16, 1915: Neurotic type, good physique. Small superficial bed-sore over sacrum. No pyrexia. Visceral examination: slight albuminuria; otherwise negative. Wassermann reaction (blood) negative. Mental condition: introspective; poor emotional tone. Vision: acuity, right $\frac{6}{6}$, left $\frac{6}{9}$ partly; fields full; right disc normal, left shows temporal pallor. Hearing normal. Cranial nerves: fine nystagmus on lateral movement; otherwise negative. Motor.—Head and neck natural. Upper limbs: slight weakness and spasticity, right and left; no intention tremor or ataxia. Trunk: weak with some rigidity of abdominal muscles. Lower limbs: almost complete spastic paralysis in extension with frequent flexor spasms. Sensory.—Subjective: girdle sensation. Objective: cutaneous sensibility perfect; vibration abolished in both lower limbs and pelvis; no loss of deep sensation in arms or hands. Sphincters: incontinence of urine and fæces; feels "call" and passage. Gait: impossible. Reflexes: all tendon jerks greatly exaggerated: all abdominals absent; both plantar responses extensor.

Progress: Two months later *in statu quo*.

Note: Duration ten years; remittent type; recent complete paraplegia.

Case XXX.—A. K., girl, aged 16. Admitted to St. Thomas's Hospital on June 22, 1915.

Family and past history good.

History of present illness: Five weeks ago in the course of three days she developed shaking of the hands, drunken gait, attacks of vertigo and headache. The left thigh felt numb and she had pins and needles in both feet. During the past week the tremor of the arms has nearly disappeared. No ocular or sphincter trouble.

On examination, June 22, 1915: Good type and physique. Visceral exami-

nation negative. Wassermann reaction (blood) negative. Mental condition, vision and hearing: normal. Cranial nerves: fine, rapid nystagmus on lateral movements; otherwise negative. Motor.—Head and neck normal. Upper limbs: slight weakness of left grip; no spasticity or wasting; coarse static tremor of hands; no true intention tremor or ataxia. Trunk good. Lower limbs: good tone; some weakness of dorsiflexion at both ankles; both limbs show tremor on sustained efforts. Sensory.—Subjective: numbness of both legs, right > left. Objective: normal except for diminution of vibration sense below right knee. Sphincters natural. Gait: a little reeling and lurching; steps unequal in length and direction; no spasticity or Rombergism. Reflexes: all tendon jerks exaggerated; upper abdominal reflexes present, lower absent; right plantar response indefinite, left extensor.

Progress: One month later the gait was almost normal, but the reflexes were unchanged. After-history could not be traced.

Note: Early case; sudden onset tending to recovery.

Case XXXI.—A. C., girl, aged 20. Admitted to St. Thomas's Hospital on June 24, 1915.

Family and past history: Nothing to note; patient is an only child.

History of present illness: Two years ago she suddenly developed a squint in the right eye with diplopia, headache, vertigo, and a tight feeling round the waist. A fortnight later she was well again. Six months later she had a precisely similar attack of the same duration. Two weeks later she had severe pain in the back of the neck and vomited; the following day the the right arm and leg were weak, she saw double, and when she closed her eyes felt as if she were moving round and round. She also had difficulty in holding her head straight, and in passing her water.

On examination, June 24, 1915: Poor type and physique; bad teeth, adenoid facies; pulse and temperature normal. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition and vision normal. Hearing: normal on right; watch heard at 6 in. on left; bone conduction > air; perforation of left drum; no mastoid tenderness; no tinnitus. Cranial nerves: weakness right external rectus with diplopia; fine nystagmus on looking to left, slow and coarse on looking to right; slight tenderness right lower face. Motor.—Head and neck: the head is carried down with chin to the left; the head can be lifted but quickly assumes this "forced" attitude; no weakness or rigidity. Upper limbs: slight weakness with some flexor rigidity of right arm; all movements of the right arm are remarkable for the slowness both of their initiation and execution; attempts at rapid movements slow intention tremor and hypermetria; left arm normal. Trunk good. Lower limbs: slight extensor spasticity on right, with weakness of dorsiflexion at ankles; left normal. Sensory.— Subjective and objective, normal. Sphincters: definite hesitancy of micturition. Gait: spastic weakness of right leg with circumduction at hip. Reflexes: all tendon jerks exaggerated,

right > left ; abdominals absent on right, just obtained on left. Right plantar response extensor, left flexor.

Progress: Two weeks later the attitude of the head was normal, and the right hemiparesis was less marked. The diplopia persisted.

Note: Remittent type with acute exacerbations.

Case XXXII.—F. L., man, aged 37, ex-soldier. Admitted to St. Thomas's Hospital on June 27, 1915.

Family history good.

Past history: Always enjoyed good health. Fourteen years ago he had a soft chancre, for which he was treated, but not with anti-syphilitic remedies ; married ; wife has had two healthy children, and no miscarriages.

History of present illness: Eighteen months ago while out walking the left foot became numb and weak, and his left hand useless, so that he could not distinguish articles in his left hand trousers pocket. The next day he had diplopia, which persisted for two weeks. The condition of the left arm improved, but his leg got worse, his walking became unsteady, and he lost control over his bladder, and to a less extent over his rectum, sometimes having incontinence and at others retention ; he was also unable to feel the passage of urine but was conscious of a "call." Three months after the onset he rapidly improved, and could walk two or three miles without feeling anything amiss in the left leg ; beyond that distance his leg would drag. The sphincter trouble almost disappeared. Nine months ago he relapsed again, his left arm and leg became weaker, he got progressively more unsteady on his legs, and again lost control over his sphincters. He also experienced various odd sensations ("tight feelings") all over his body and limbs, fleeting in character, and became subject to attacks of rotatory vertigo without sickness or tinnitus. A month ago his condition underwent temporary improvement, but his walking is now worse than ever, especially in the dark.

On examination, June 27, 1915: Good type and physique ; no evidence of past syphilis. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition: vision and hearing normal. Cranial nerves: no ophthalmoplegia ; rather coarse nystagmus on lateral movements ; slight but definite dysarthria, slurring, halting, staccato. Motor.—Head and neck normal. Upper limbs: right normal ; slight weakness of extensors on left, but no rigidity ; no tremor or cerebellar ataxy ; slight sensory ataxy on left with tabetic athetosis. Trunk good. Lower limbs: slight extensor spasticity with weakness of flexors on left ; sensory ataxy of both legs ; no loss of power on right. Sensory.—Subjective: girdle sensation and numbness of left leg. Objective: cutaneous sensibility is lost or impaired down back of left lower limb, sacral segments 1 to 5 ; otherwise normal. Deep sensation: slight loss of passive position and movement in left hand and wrist, compass threshold raised on left (1·5 cm. left palm, 0·75 cm. right palm), partial astereognosis left hand. Moderate loss of sense of position and movement, especially peri-

pherally in lower limbs, left > right, but not sufficient to account for the high degree of inco-ordination. Vibration impaired in left pelvis, but within normal limits elsewhere. Sphincters: difficulty in feeling passage of urine and fæces; hesitancy of micturition alternating with urgency; anal reflex present; absolute loss of sexual power. Gait: can just walk a few steps unaided; Rombergism present; the gait is ataxic and reeling and combines the features of both tabetic and cerebellar inco-ordination. Reflexes: all tendon jerks increased, legs > arms. All abdominals absent. Both plantar responses extensor.

Progress: Three weeks later *in statu quo.*

Note: Remittent type with little tendency to the formation of lesions in fresh localities; involvement of cord in sacral region.

Case XXXIII.—F. T., man, aged 30, policeman. Admitted to St. Thomas's Hospital on July 7, 1915.

Family and past history good.

History of present illness: Two years ago he noticed a mist in front of his left eye, which has persisted. Nine months ago his legs quite rapidly became weak and he had difficulty in getting about. His walking has varied considerably since then, but on the whole it has got worse. Eight months ago he developed urgent micturition with occasional "accidents." More recently he has noticed numbness down his legs and his speech has got slow and jerky. Recently the sphincter trouble has improved; no "accidents" lately. Never diplopia, tremor, or emotionalism.

On examination, July 7, 1915: Good type and physique. Visceral examination negative. Wassermann reaction (blood) negative. Mental condition and hearing normal. Vision: acuity, $\frac{6}{6}$ right and left: large central scotoma in left eye, involving fixation point, especially to colours; left disc is pale all over, edges clear; right disc normal. Cranial nerves: no nystagmus or ophthalmoplegia; slight ataxic dysarthria, slow, staccato, and explosive. Motor.—Head and neck, trunk, upper limbs, normal; no tremor. Lower limbs: slight extensor spasticity and weakness of flexors, left > right; no ataxy. Sensory.—Subjective, numbness in legs. Objective, normal. Sphincters; urgent micturition. Gait: spastic; no Rombergism or ataxy. Reflexes: all tendon jerks exaggerated, legs > arms; all abdominals absent; both plantar responses extensor.

Progress; No material change four weeks later.

Note: Remittent type in early stages tending to become slowly progressive.

Case XXXIV.—C. R., woman, aged 25, married. Admitted to St. Thomas's Hospital on November 16, 1920.

Family history unimportant.

Past history: Since the age of 14 has been subject to attacks of headache and giddiness, with vomiting, diarrhœa and faintness.

History of present illness: Four years ago a few hours after having had

some teeth out under gas she "came over queer" and was unable to see or speak for some minutes: the next day her walking was unsteady. This unsteadiness has persisted off and on ever since, but varies a great deal; for weeks together she will walk as if drunk, and then get nearly well again. She is always much worse in the dark. Three years ago the right hand suddenly became useless; she could move it but could not feel things properly with it. After six weeks it improved, but has never got quite well. Twelve days ago she woke up to find that she was cold and numb all down the left side, and her left arm was useless although not paralysed: the left leg seemed weak and her walking more unsteady than ever. She also felt as if she had a tight band round her waist. Four days later she felt as if hot water were being poured down her left side. Recently she has had attacks of rotatory vertigo. Never speech disturbance, diplopia, or sphincter trouble.

On examination, November 16, 1920: Good type. General condition good. Thoracic and abdominal viscera negative. Wassermann reaction (blood) negative. Mental condition: rather sanguine and optimistic, but no loss of emotional tone; condition is not abnormal. Vision normal in every particular. Hearing normal. Vertigo: objects move from left to right. Cranial nerve normal, no nystagmus. Motor.—Head and neck normal. Upper extremities: no loss of power on right or intention tremor; slight tabetic athetosis of right hand and some sensory ataxia; power on left is subnormal, but with eyes shut this defect is greatly accentuated; wild sensory ataxia on left. Trunk: good. Lower extremities: right normal except for slight spasticity; left, considerable spasticity with weakness, especially of flexors. Sensory.—Subjective: paræsthesiæ trunk and left arm and leg. Objective: cutaneous sensibility, everywhere perfect. Profound loss of deep sensation in left upper limb; she has no idea of the position of the limb and loses it in bed; no threshold to compasses, complete astereognosis; localization perfect, vibration impaired below left elbow. Slight astereognosis in right hand and raised threshold to compasses (2·5 cm.). In the left lower limb there is some disturbance of sense of passive posture and movement with loss of vibration reaching up to the left pelvis; vibration much diminished in right pelvis and lower extremity. Sphincters natural. Gait: spastic and ataxic; Rombergism present: no cerebellar inco-ordination. Reflexes: all jerks increased, especially in legs; abdominals all absent: both plantars extensor.

Progress: Two months later (January, 1921) the condition had greatly improved; the loss of deep sensation in the left arm was diminishing, she no longer loses the limb, and could use a fork in the left hand and dress herself. Reflexes unaltered. April, 1921: improvement maintained; no loss of passive position and movement is demonstrable in left arm, there is no sensory ataxy, and the patient says that this limb is now better than its fellow. The gait is much improved, the right plantar response is flexor and the left extensor.

Note: Remittent type, lesions appear almost confined to spinal cord; remarkable recovery from most recent lesions.

Case XXXV.—L. H., woman, aged 25, domestic servant. Admitted to St. Thomas's Hospital on November 10, 1920.

Family history: Mother very "nervous"; one sister has had chorea.

Past history: Nothing of importance.

History of present illness: Ten years ago she woke up one morning to find that her right arm was useless and her right leg was weak. The leg got well in a few days, but the arm remained bad for four months; it was not paralysed, but felt numb and cold, and she could not use it properly. Ever since she has been subject to paræsthesiæ in the right arm and leg. Six years ago she suddenly developed an internal squint in the left eye and saw double: this condition persisted for three weeks and then passed off. Five years ago after an attack of influenza her legs became weak and her walking unsteady; complete recovery in six weeks. Three years ago her legs began to get weak again, and she had pain in her legs and pins and needles round her ankles. Her walking gradually became worse, so that her feet dragged and she had to go about with the aid of a stick. The weakness of the legs has varied considerably in the past three years, but has never entirely disappeared. Latterly the legs have felt cold and numb. Two months ago she again saw double, and a little later experienced pain behind the eyes, especially the left, which rapidly became blind; the vision is now returning but things "look black out of the left eye." During the past three weeks she has been subject to attacks of rotatory vertigo. No affection of speech or sphincters.

On examination, November 10, 1920: Thoracic and abdominal viscera negative. Wassermann reaction (blood) negative. Mental condition normal, perhaps a trifle sanguine. Vision: right, acuity $\frac{6}{9}$, fields normal, temporal pallor of disc; left, acuity $\frac{6}{36}$, large scotoma, disc edges all blurred, swelling 1·5 D.; no hæmorrhages (retro-bulbar neuritis). Hearing normal. Cranial nerves: pupils normal; weakness left external rectus; well-sustained horizontal nystagmus; otherwise negative. Motor.—Head, neck, trunk, and upper extremities, nothing to note. Lower extremities: slight spasticity, weakness of all flexors; loss of power is greatly accentuated if legs are screened from view during testing; considerable ataxy of tabetic type. Sensory.—Subjective: numerous paræsthesiæ, especially in lower limbs. Objective: cutaneous sensibility everywhere normal; no loss of deep sensation in upper limbs; vibration—complete loss below knees, profound loss in femora and pelvis; sense of passive posture and movement gravely disturbed in lower limbs, especially peripherally. Gait ataxic and spastic; Rombergism present. Sphincters natural. Reflexes: arm-jerks brisk; knee-jerks greatly exaggerated; ankle-jerks diminished; all abdominals absent; both plantars extensor.

Progress: Two months later the vision in the left eye was $\frac{6}{12}$, the scotoma had contracted, and there was no œdema of the disc, which was pale all over. The diplopia had disappeared, the legs were stronger, and the walking had improved. The right plantar response was less definitely extensor than on admission.

Note: Markedly remittent type with exacerbations and recoveries.

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THE EXPERIMENTAL STUDY OF DISSEMINATED SCLEROSIS.

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THE history of the experimental study of disseminated sclerosis begins with the publication of a paper by myself [1] in 1913. The paper was a report of experiments in which rabbits and one cat were injected with cerebrospinal fluid, filtered and unfiltered, taken from a rapidly progressing case of the disease. Several of the rabbits became paralysed and the conclusion was drawn that disseminated sclerosis is caused by a filter-passing organism, or by a water-soluble poison present in the cerebrospinal fluid.

The results of the experiments have been confirmed by Kuhn and Steiner [2], Simons [9], Marinesco [5] and by Rothfeld, Freund and Hornowski [7].

Kuhn and Steiner were able to transmit the disease to guinea-pigs as well as to rabbits; in one set of experiments they achieved four successful passages through guinea-pigs and, in another set, two through rabbits. This constituted a notable advance and provided solid grounds for the belief that disseminated sclerosis is an infectious disease. More important still, they observed a spirochæte in the blood of the paralysed rabbits and guinea-pigs. The organism was described as resembling closely the leptospira of Weil's disease; it could be stained with Giemsa's stain and with Loeffler's flagella stain, and was blackened in tissues by Levaditi's silver method. Kuhn and Steiner have put forward the claim that the spirochæte they describe is the essential ætiological agent in multiple sclerosis.

Siemerling [8] observed a similar organism post mortem in the cerebral lesions of a patient who suffered from disseminated sclerosis, but who died of an intercurrent facial erysipelas.

Rothfeld, Freund and Hornowski, in a critical paper, give an account of the transmission in series of nervous disorders in rabbits and guinea-pigs. These authors made an exhaustive bacteriological and histological study of the animals which were killed or which died in the

course of their work. The bacteriological results were uniformly negative; they were unable to find Kuhn and Steiner's spirochæte, though all the usual methods of search were employed. The chief pathological features of their animals were the frequent occurrence of coccidiosis, pulmonary inflammatory lesions, cellular infiltration of the kidneys and of tuberculosis. The failure to find a spirochæte and the frequent occurrence of coccidiosis and of inflammatory lesions led the authors to reject the obvious conclusion that the transmission of paralysis in series—beginning with cerebrospinal fluid as the primary inoculum, and continuing with organ emulsions from affected animals—was evidence of the existence of a living virus in the cerebrospinal fluid; they consider that the close analysis of the anatomical pathological findings—the non-specific character of the changes found, the constantly negative bacteriological results, the fact that the intensity of action of the inoculum gets weaker in successive passages and that in some of their animals disease and death were caused by (or associated with) coccidiosis or tuberculosis—points definitely against the simpler interpretation. The difficulties met by these authors are inevitable in such experiments, and, of course, compel caution in drawing conclusions. But there are other and more likely fallacies in the work, as will be shown later. The substance of the published work may thus be divided into two parts: first, the transmission in series to animals; and secondly, the discovery of a spirochæte in affected animals and the observation of a similar organism in the cerebral lesions of man. The first part only will be discussed in this paper. The second part, together with the histological changes in the affected animals, will be dealt with later.

Experimental.

During the past twelve months I have injected rabbits and in a few instances guinea-pigs with cerebrospinal fluid obtained from twenty-one cases of disseminated sclerosis. All the cases were carefully selected from a large number of patients and each exhibited some or all of the classical signs of the disease, namely, partial or complete paralysis, with Babinski's sign, nystagmus, intention tremors and staccato speech. The cerebrospinal fluid in every case gave a negative Wassermann reaction: for carrying out the test in a number of cases I am indebted to Dr. Paul Fildes.

The total number of rabbits injected was 129, and of guinea-pigs 15. The guinea-pigs remained in good health and none ever showed

signs of paralysis; 17 of the rabbits became ill and paralysed and 112 remained in good health, or if they became ill or died the cause was not clearly connected with the experimental injection.

Of the twenty-one sets of experiments in which rabbits were injected with cerebrospinal fluid—the numbers varied from two to six in the experiments—fourteen were completely negative or, when illness occurred, there were such complications as diarrhœa or extensive coccidiosis. Under such circumstances the experiment was written off as negative.

The seven sets of positive experiments may be divided into groups of four and three respectively. In the first group attempts to transmit the disease in series failed; in the second group transmission for two or more passages was successful. Two of these experiments will be given at length.

Case No. 4.—The patient, K. B., a girl of 18, was lumbar-punctured on August 3, 1920. The cerebrospinal fluid issued under pressure and was clear and colourless; the cell count was not increased.

On the same day four young rabbits and two guinea-pigs were injected with the fluid. Rabbit 1 received ¼ c.c. subdurally; Nos. 2 and 3, ½ c.c. into the thigh muscles; No. 4, 1 c.c. subcutaneously. The guinea-pigs were injected intramuscularly and subcutaneously, each with 1 c.c. Rabbits 2, 3 and 4 and both guinea-pigs remained in good health and were killed three months later. On the morning of August 6, Rabbit No. 1 was noticed to be ill and weak in the fore-limbs, the animal was unable to hold up its head, which was wet and soiled with the morning's feed. The animal got rapidly worse and was killed in the afternoon of the same day. Post mortem nothing abnormal was noticed in the thorax and abdomen; the surface of the brain was redder than usual. Cultures were made in broth and serum broth from the heart blood and the brain: they remained sterile for seven days. Cerebrospinal fluid was taken aseptically from the fourth ventricle diluted, and injected subdurally into two normal rabbits. Pieces of brain were excised, minced with sharp scissors and injected intraperitoneally in doses of ½ c.c. into four rabbits.

Of the six rabbits inoculated four remained in good health; they were the two which had been injected subdurally with cerebrospinal fluid and two of the four which had received brain emulsion intraperitoneally. Of the two remaining animals one was found dead on the morning of August 8; extensive coccidiosis was found post mortem and the animal was discarded.

The remaining rabbit remained in good health until August 12, when it was noticed to be quiet. On the following day it was found dead. The course of the illness was thus not observed.

Post mortem.—Heart and lungs were normal. The liver and spleen were small. The inoculum of brain emulsion was found and films made from it were stained for bacteria, and none were found. The surface of the brain was deep pink in colour; on section no hæmorrhages were found. Heart blood culture was negative.

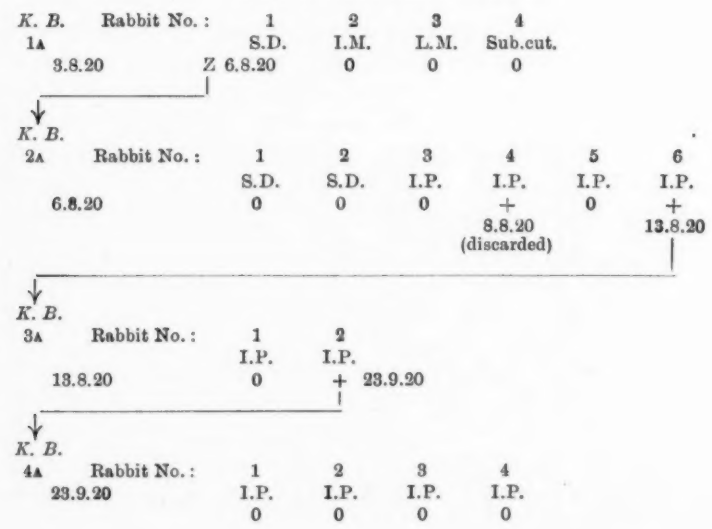
Two rabbits were injected intraperitoneally with an emulsion of brain; one of the animals remained in good health, the other died on September 23.

Post mortem.—Nothing abnormal was found in the thorax: in the abdomen there was a large excess of clear colourless fluid, which clotted after incubation for one hour at 37° C. The surface of the brain was congested.

Four rabbits were inoculated intraperitoneally with the brain; they remained in good health and were killed three months later.

The course of the experiment is summarized in the following chart, where O indicates that the animal remained in good health, + signifies died, and Z means killed.

CHART I.—*K. B.*, AUGUST 3, 1920.



Case No. 6.—The patient (M. K.) was a woman aged 36, who had suffered from disseminated sclerosis for four years. She was unable to walk; the legs were contracted. A lumbar puncture was made on September 3, 1920. The fluid poured out copiously and was clear and colourless. There was no excess of cells; the Wassermann reaction was negative.

On the same day six rabbits and four guinea-pigs were injected with the cerebrospinal fluid. The guinea-pigs remained in good health and were killed after three months. Of the rabbits three were injected into the muscles of the thigh, one was injected intravenously, one intraperitoneally and one intra-ocularly. Only the last rabbit eventually showed any symptoms, the other five remaining in good health.

The animal which had been inoculated intra-ocularly was found ill and paralysed on the morning of September 27; it got worse during the day and was killed in the afternoon. Post mortem nothing abnormal was found in the thorax; in the abdomen, a moderate degree of coccidiosis. Four normal rabbits were injected with brain emulsion.

Of these four rabbits one died during the week-end, October 20, and was thrown away.

On October 27 one was found paralysed and dying; this animal had been distinctly ill from October 20. Post mortem the heart and lungs were normal; the liver was small, the stomach empty, the bladder was enormously distended with urine and the large intestine full of fæces. The brain surface was pink. Heart blood cultures remained sterile for seven days.

Five normal rabbits were injected intraperitoneally with an emulsion of the brain. The course of events in these rabbits may be seen in Chart II, from which it will be noted that all the animals became affected and were killed or died. One, however, No. 5, suffered from diarrhœa and was found post mortem to be extensively affected with coccidiosis. This animal must therefore be disregarded.

The rabbit from which the next series of inoculations was made (No. 1) was ill and tremulous on November 1; the following day it was much worse, unable to raise itself or to move its limbs; the head was retracted. Post mortem nothing abnormal was found in the thorax; in the peritoneal cavity there was a large excess—amounting to 30 c.c. roughly—of clear colourless sterile fluid which clotted on standing at 37° C.

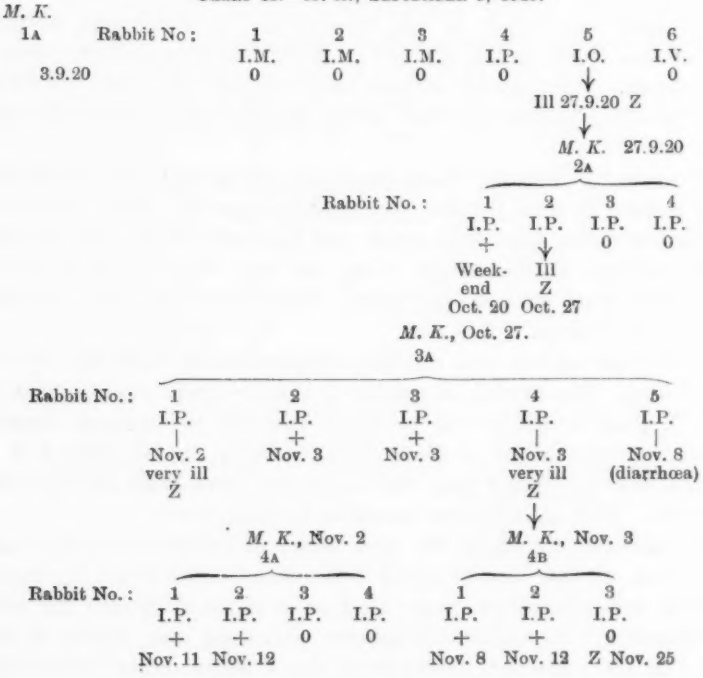
Four normal rabbits were injected intraperitoneally with an emulsion of brain; two of these survived indefinitely, and two died.

The two latter animals were examined post mortem and, as in the cases above, no obvious cause of death could be found. Cultures were made of heart blood, peritoneal exudate and cerebrospinal fluid; all were negative. Further passages were not attempted.

Another passage, 4B, was made from an animal which was killed on November 3, after an illness lasting twenty-four hours Three rabbits were inoculated: one died on November 8, and one on the 12th; post mortem examinations failed to reveal the cause of death; there was an excess of sterile fluid in the peritoneal cavity; the heart blood and cerebrospinal fluid were sterile. The third rabbit was killed on November 25 for another purpose; it had shown no signs of disease.

The experiment is summarized in Chart II.

CHART II.—*M. K.*, SEPTEMBER 3, 1920.


M. K.
1A
3.9.20
Rabbit No: 1 2 3 4 5 6
I.M. I.M. I.M. I.P. I.O. I.V.
0 0 0 0
Ill 27.9.20 Z
M. K. 27.9.20
2A
Rabbit No.: 1 2 3 4
I.P. I.P. I.P. I.P.
+ 0 0
Week-end Oct. 20
Ill Oct. 27 Z
M. K., Oct. 27.
3A
Rabbit No.: 1 2 3 4 5
I.P. I.P. I.P. I.P. I.P.
Nov. 2 very ill Z
+ Nov. 3
+ Nov. 3
Nov. 3 very ill Z
Nov. 8 (diarrhœa)
M. K., Nov. 2
4A
M. K., Nov. 3
4B
Rabbit No.: 1 2 3 4 1 2 3
I.P. I.P. I.P. I.P. I.P. I.P. I.P.
+ + 0 0 + + 0
Nov. 11 Nov. 12 Nov. 8 Nov. 12 Z Nov. 25

DISCUSSION.

It has been found that rabbits injected with cerebrospinal fluid taken from cases of disseminated sclerosis have in some instances

developed an illness accompanied by paralysis; in the two sets of experiments reported, one rabbit out of four in one experiment and one out of six in the other became affected. The injection into normal rabbits of minced brain from the paralysed animal has led to the development of a similar kind of illness, and this has been carried through four passages.

As in the experiments of Rothfeld, Freund and Hornowski already referred to, the simplest interpretation of these results is to assume the existence of a living virus, which is pathogenic to rabbits, in the cerebrospinal fluid; the virus becomes located in the brain, whence it may be carried to other rabbits in series.

It would be rash, however, to draw this conclusion from such a small number of experiments without proper controls—which have to be discussed—unless definite ocular or cultural evidence of the existence of an organism in the cerebrospinal fluid could be provided. At best, such experiments on rabbits can lead only to conclusions of probability, though where a *virus fixe* has been obtained, as in the recent work on encephalitis lethargica, the probability becomes a practical certainty. But up to the present a *virus fixe* has not been obtained in work on disseminated sclerosis.

The alternative explanation which Rothfeld, Freund and Hornowski have offered for such results is not more than a remote possibility. The naked-eye post mortem findings in rabbits which have died in the course of the experiments recorded above differ only in the following particulars from what has been found in post mortems made during the same period on normal animals which had been killed for various purposes; namely, the constant slight congestion of the surface of the brain, clear peritoneal exudate, and the occurrence of small hæmorrhages in the spinal cord and brain. That is to say, it has not been possible to explain the illness and paralysis by means of gross anatomical changes or of infections. Where extensive coccidiosis has been found in an experimental common animal, the animal has been disregarded. The existence of diarrhœa, often a sign of coccidiosis, has throughout been regarded as of sufficient importance to warrant rejection of a rabbit. The microscopic evidence of inflammatory lesions in the lungs and kidneys of rabbits is stressed excessively by Rothfeld and his co-workers; such changes can be found in almost any rabbit and in animals killed roughly may amount to naked-eye hæmorrhages [7].

A much more important criticism of all this experimental work can

be founded on the well-established fact that rabbits especially and guinea-pigs to a less extent are prone to spontaneous paralysis. The frequency with which this occurs has, in my experience, varied considerably in different laboratories. But there is no doubt that wherever large numbers of rabbits and guinea-pigs are kept cases of paralysis are observed from time to time. As an illustration of the commonest form the following case will be given in some detail.

A healthy young rabbit (1 kilogram), one of a series of six which formed part of a feeding experiment just begun, was recorded in the laboratory book as in good health at 10 o'clock in the morning; at noon it was found completely paralysed in the hind limbs. The rabbit was not ill, it was anxious for food and responded when touched. At 2 p.m. it was killed with coal gas. Post mortem nothing abnormal was found in the thorax; in the abdomen a moderate degree of coccidiosis of the liver was noted and the bladder was enormously distended with clear urine. Examination of the spinal column revealed a fracture at the level of the 11th dorsal vertebra: the spinal cord at this level was contused and infiltrated with blood. It was impossible to discover how the rabbit came by the accident.

I have studied the clinical conditions and the post mortem findings of most of the cases of spontaneous paralysis—between twenty and thirty—in normal rabbits occurring in the laboratories of the National Institute during the last twelve months. The principal clinical features of these cases have been, first, the suddenness in onset; secondly, the paralysis is the principal condition, the rabbits often being otherwise perfectly healthy; thirdly, the paralysis is always of the hind limbs only; fourthly, the animals sometimes recover, and when left they may live for weeks or even months until ascending infection of the urinary tract or persistent incontinence of fæces compels one to kill them. Post mortem examination generally reveals some gross morbid condition to account for the paralysis. The commonest pathological conditions which I have found in such animals is fracture of the spine. In two cases an abscess involving the spinal column was found; one was in a guinea-pig and one in a rabbit. Films of the pus were stained for the tubercle bacillus and were negative. A tape-worm cyst of the spine muscles was found in one animal; in another no gross lesions were discovered, but section of the hardened spinal cord showed scattered small hæmorrhages. The clinical features of this last animal were such as have already been described.

In rabbits which become paralysed after the injection of cerebro-

spinal fluid the paralysis is not the dominant feature; it is only part of a severe and general illness, which, as a rule, progresses very rapidly, but may sometimes be detected for several days before the animal is seriously ill. The clinical differences between these cases of experimental paralysis and the spontaneous cases are so great and constant as to lead me to conclude that they are essentially different in origin. The post mortem findings support this conclusion.

Another fact which must be borne in mind in drawing conclusions from the experimental work on disseminated sclerosis is the infrequency of successful experiments. In the series reported above one rabbit only in four in the first experiment and one in six in the second showed symptoms. This result corresponds with what other observers have published. It is, however, not difficult to understand. The organism, if there be one, is not constantly present in cerebrospinal fluid and is never present in large numbers. In tubercular meningitis it is the exception rather than the rule to find tubercle bacilli in the cerebrospinal fluid and in general paralysis of the insane the spirochæte of syphilis is not often found. Moreover, differences in susceptibility are easily brought out when the inoculum contains a small number of organisms.

The necessary control experiments for this work have not yet been carried out, namely, the inoculation of a large number—say 100—of rabbits, with the cerebrospinal fluids of persons certainly not suffering from multiple sclerosis. Simons controlled his work in this way, but the number of his experiments was small.

The effects of the injection of normal rabbit brain into a normal rabbit have been studied by Remlinger [6], who found that in 100 rabbits thus treated—sometimes with "enormous quantities"—only one animal exhibited symptoms of paralysis. Remlinger gives a description of the clinical condition of this animal which corresponds very closely with what has been stated above. His observations serve to exclude the possibility that the second and later passages of the experiments given in this paper are fallacious.

The conclusion drawn from the work is, therefore, that disseminated sclerosis is probably an infectious disease and that the virus may sometimes be found in cerebrospinal fluid.

I am indebted to Drs. A. G. L. Reade, Wilfred Harris and George Riddoch for permission to take cerebrospinal fluid from the patients under their care.

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REPORT ON A CASE OF MYOCLONIC ENCEPHALOMYELITIS OF MALARIAL ORIGIN.

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EPIDEMIC encephalitis, the existence of which was at first denied by certain authors, has ended not only in establishing its existence but also in invading the domain of a large number of organic diseases, as is shown by the report of the Local Government Board and the observations of French authors, notably those of Netter. We admit, and we are right in doing so, that the localization of the virus in different segments of the central nervous system can produce the clinical aspect of Parkinson's disease, hebephrenia, catatonia, chorea, myoclonus, &c. It is evident that even if epidemic encephalitis can simulate in a striking manner Parkinson's disease, as proved by Longues, Sicard, and Pierre Marie, one will always be able to find differences between the signs of the "Parkinsonism" of encephalitis and true Parkinson's disease, as Pierre Marie and Mlle. Levi have shown. As a matter of fact, in spite of the apparent resemblance between "Parkinsonism" and Parkinson's disease, the mode of onset of the former, the cause of the affliction, and the character of the symptoms permit us easily to distinguish the one from the other.

Furthermore, as our knowledge of the disease and the conditions which produce it advances, we shall find with certainty that it is confused with other pathological conditions which do not belong to it, as for example hysteria (Georges Guillain, personal observation), tubercular meningitis; even the myoclonic form of encephalitis, to which von Economo and Sicard have attracted attention, can be simulated by hysteria and different infections, amongst which should be included malaria.

I propose in this paper to bring anatomo-clinical proof in favour of this opinion. I will give first of all a detailed account of my observations of the disease and of lesions which we have found in the nervous system, and will then state the lessons which can be learnt from our anatomical and clinical observations.

The case was that of a woman, aged 26 years, who was taken ill on September 3, 1920, suffering from fatigue, anorexia and fever of an indefinite type. She remained in bed for two weeks, and as her condition grew worse she entered a hospital, where she remained for only a few days. At this time she was feverish and unable to walk, and one noticed that she had slight convulsive movements of the limbs and of the face. On September 27 she was transferred to our wards, and we noticed that the skin was pale, and that she could neither walk nor stand up. Speech was difficult and dysarthric. Lying on her back one noticed in the upper limbs almost continuous involuntary movements, accentuated at the extremities. These movements showed themselves in the form of rapid oscillations, which consisted of flexion and extension of the fingers or abduction and adduction, whilst in the arm and forearm the movements were of a more myoclonic type without displacement of the limbs. From time to time the movements of the upper limbs were quickened, and were transmitted to the trunk, which was agitated by contractions rhythmical in character. On the side of the abdomen there were sharp contractions having the same rhythm as the respirations (20 per minute). Respiration was regular but superficial, and at times the patient took deep inspirations. There were rapid lateral movements of the head, and at the same time rhythmic movements of the jaws, the lower jaw coming together in such a manner that there was a gnashing of teeth. The eyes were moved laterally and vertically so that they appeared as if they rolled in the orbits. The eyelids fluttered rapidly, the facial muscles twitched, and the nostrils dilated and contracted.

In the lower limbs the involuntary movements consisted of rapid sharp contractions localized to the thigh muscles. Movements were less frequent in the muscles of the leg. The big toes were in a state of continuous extension, though from time to time they also showed rhythmic movements.

To sum up, the majority of the voluntary muscles were subject to involuntary movements so rapid that one could not count them; they were myoclonic in appearance, more accentuated in the extremities of the upper limbs, in the jaws, and in the orbit. Further, the muscles of the trunk showed movements, larger in size and less frequent, which were from time to time transmitted to the arms. Beside these movements, which were accompanied by slight displacement of the segments in which they took place, one noticed very rapid muscular contractions.

The tendon reflexes of the limbs were abolished; the pupils were equal and reacted to light and accommodation; the cutaneous reflex of the abdomen and even the plantar reflex were absent.

At the level of the right parotid gland was a swelling of considerable size which was painful.

The pulse was so rapid that it could not be counted at the wrist; the femoral pulse beat at 150 to the minute.

The patient had a slight rigidity of the neck and a suspicion of Kernig's sign. The limbs showed no contractures. The temperature was higher in the morning (38·6° C.) than in the evening (37·4° C.).

On the day of the entry into hospital (September 27, 1920) we wished the patient to get up for the operation of lumbar puncture and to seat herself in a chair; but during this manœuvre she fell into a kind of syncope, the tremblings ceased and her arms fell inert beside her body.

When she had been placed upon the bed it was noticed that her pulse was imperceptible and that respiration had apparently ceased.

Artificial respiration was performed and her respiration was restored, although the pulse remained very feeble. Presently the tremor reappeared little by little and in a few minutes regained its previous intensity.

During the day and night the patient was in a state of delirium.

Lumbar puncture, carried out in the lateral position, showed ten lymphocytes by division (Nageotte) and the blood an intense mononuclear leucocytosis.

The urine was brown and on boiling a thick cloud of albumin appeared. Vidal's reaction and the Weil-Felix test were negative.

On September 28 the temperature rose to 39° C., and the state of the patient became much worse. Respiration became noisy, and she died suddenly at 2 p.m. Just before her death the involuntary movements described above disappeared.

As the patient died almost suddenly we were not able to pursue all our investigations for the purpose of arriving at a correct diagnosis, but from the clinical aspect, the slight fever, and the indefinite lymphocytosis, we thought that we had to deal with a case of epidemic encephalitis of myoclonic form; but examination of the blood, followed by the study later of the alterations in the central nervous system, revealed our mistake. In fact there was revealed in the blood, in addition to the lymphocytosis, the presence of hæmatozoa and even of crescents (fig. 1).

On macroscopic examination the brain had already attracted our attention by its greyish coloration, and besides one saw here and there, in addition to the hyperæmia, punctate hæmorrhages in the cortex, the corpus striatum, and especially in the grey matter of the spinal cord. The meninges were unaffected, the cerebellum was hyperæmic, and the

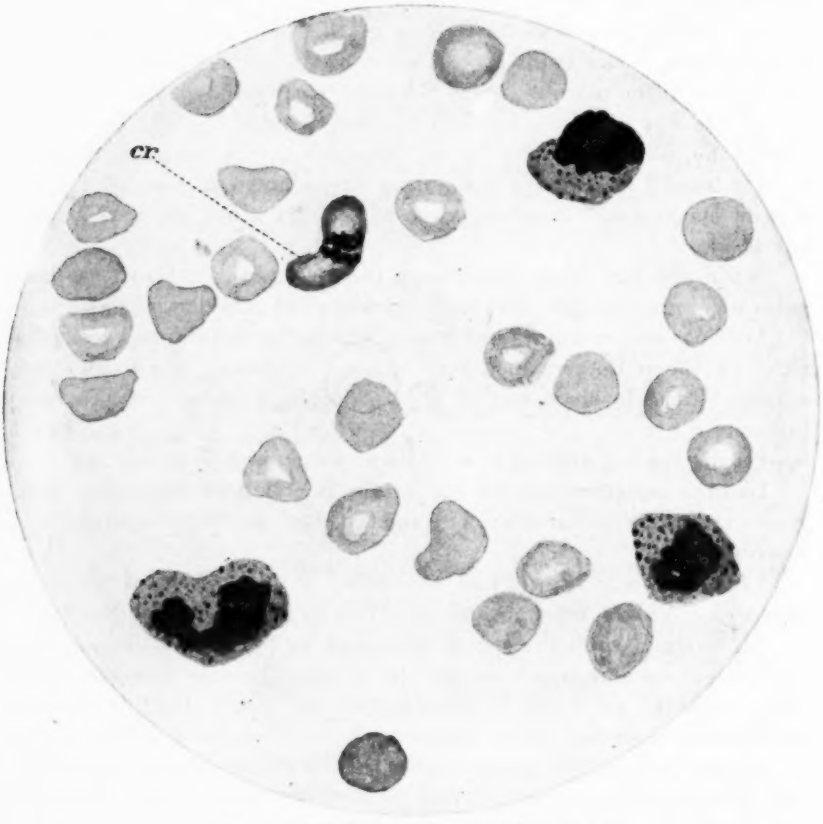

FIG. 1.—Blood-film leucocytes and crescent.

lateral ventricles were slightly dilated. The parotid gland on the right side was congested and showed signs of parenchymatous infiltration. The long narrow vessels which cross the cortex to enter the white matter were dilated and showed, for the most part in their adventitial sheath, a considerable number of lymphocytes, plasma cells, and some

mononuclear leucocytes. Here and there, in the track of precapillary vessels and venules, colonies of plasma cells and fibroblasts were seen, and a similar infiltration of the adventitial sheaths of the vessels was visible in the white matter. Small vessels cut across contained in places a large number of lymphocytes and occasionally also some pigmented mononuclear cells.

FIG. 2.—Network of capillaries of ascending frontal dilated and, containing in their interior, red corpuscles infected by the parasites and showing pigment.

In general the endothelial cells of the veins, as those of the capillaries, were swollen and sometimes even detached.

The small meningeal vessels were congested and in their sheaths a certain number of lymphocytes and mononuclear cells were recognized.

Hæmorrhages were not the rule. It was quite exceptional to see extravasations in the parenchyma, but hæmorrhagic streaks, which we saw in the spinal cord and of which I will speak later, affected also the

cerebral cortex. Nevertheless I encountered some small hæmorrhages in the cornu ammonis, where we found a thrombus of leucocytes in a meningeal vein, forming a nodule which completely filled the lumen of the vessel.

In all regions of the cerebral cortex infiltrated capillaries and veins were found, dilated or filled with lymphocytes with some mononuclear leucocytes and plasma cells in addition. Throughout on the interior of the vessels red globules were seen which had lost their colour in proportion to the development of the parasite (fig. 2) and a capillary plexus was seen to be distended by these red globules which filled the lumen of the vessel.

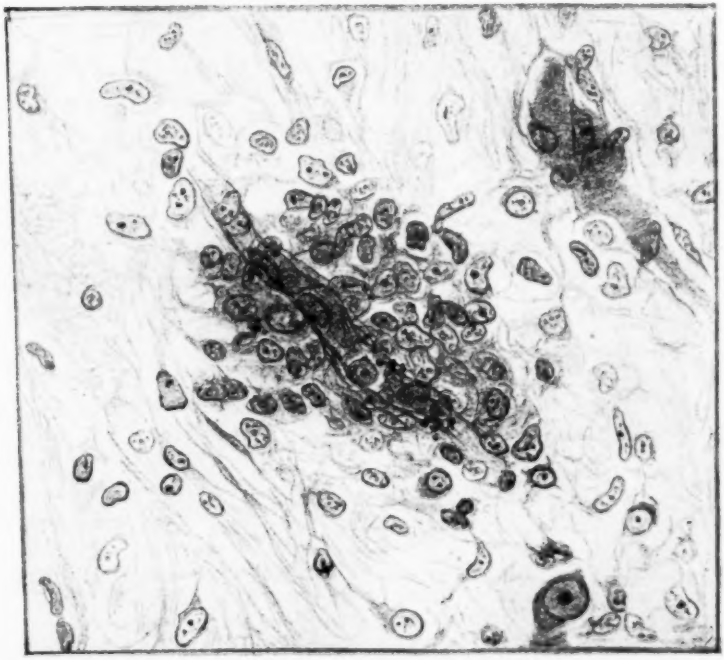

FIG. 3.—Nodule around a capillary in the olivary body; proliferated neuroglia cells.

On the surface of these globules some hæmatozoa, round in shape, were seen occupying them to a greater or less extent.

In the substance of the grey matter, as in the white matter, we remarked an hypertrophy and multiplication of neuroglia cells between

the nerve cells in the neigbourhood of the vessels or near to them. In fact we were able to count up to ten neuroglia cells in the neighbourhood of the base and of the body of the deep pyramidal cells. The same neuroglial reaction existed in the neighbourhood of the small vessels of the white substance, but here we noted a new growth of

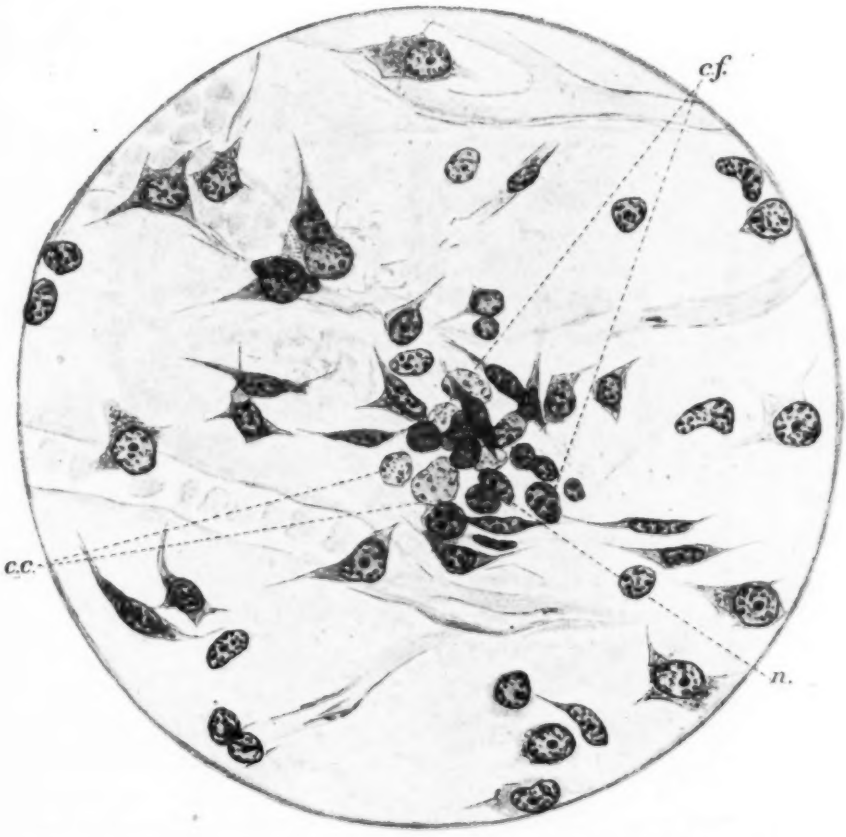

FIG. 4.—Small nodule constituted by cells with a clear nucleus and with granular nucleus

neuroglia of peculiar formation caused by the multiplication of these cells in a mass and resulting in a nodule which existed only in the deep white matter in the neighbourhood of the grey matter and which could be found in various sizes. The mean size of these nodules

was 210 μ and 130 μ and they appeared to be formed almost entirely of neuroglial cells.

But there are two reservations which must be made at this point—firstly Nissl's method is not at all satisfactory for the study of the

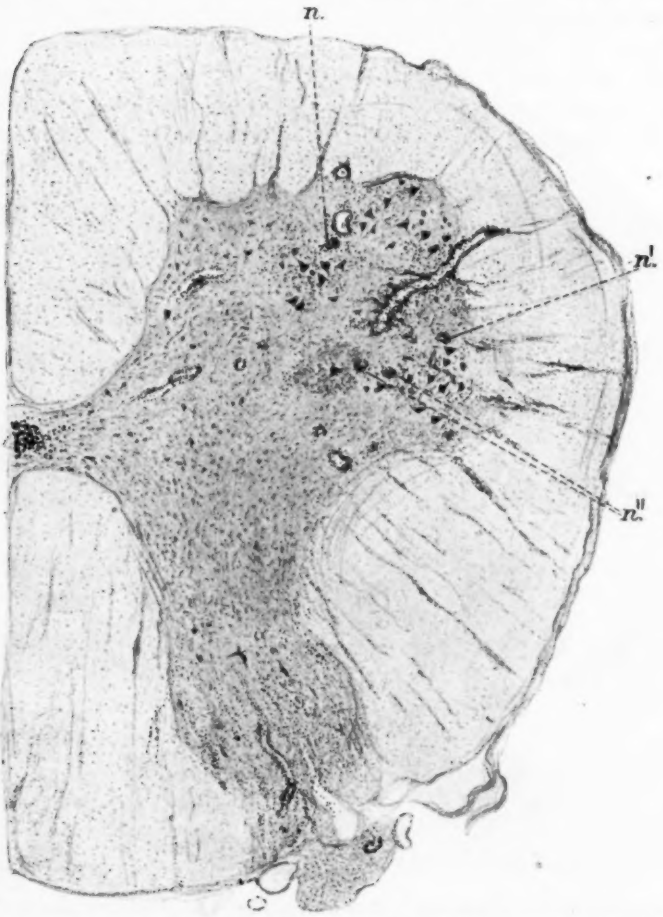

FIG. 5.—Lumbar spinal cord showing infiltration of the vessels in the grey matter and their ramifications and presence of nodules n, n', n''.

histological formation of nodules, and secondly these new growths show a different structure in the brain, peduncle, pons, bulb (fig. 3) and the spinal cord (figs. 4 and 5). One can, nevertheless, distinguish

two species of them in the nervous centres, those of loose structure in which neuroglial cells predominate and others more compact in close contact with the vessels, made up of lymphocytes, mononuclear cells and fibroblasts, to which are occasionally added some plasma cells; at their periphery are a certain number of neuroglial cells, which appear to be increased in size but not multiplied to any great extent.

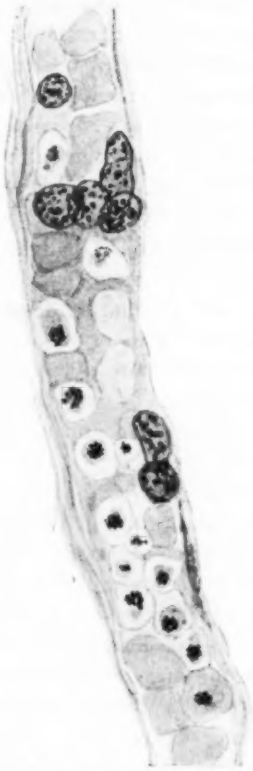

FIG. 6.—Longitudinal section of a small vessel of the grey substance of the bulb, showing in a group of lymphocytes and throughout its extent red corpuscles which have lost their colouring matter owing to the presence of the parasites.

Employing the method of Cajal for neuroglia we have unfortunately not come across (in the sections which we have examined) the nodules we found by Nissl's method; but we stained by this method some sections from a case of exanthemic typhus, and noted that, contrary to

the opinion of some authors, neuroglia played there a rôle which was entirely secondary.

Lesions almost analogous to those in the cortex were found in the optic thalamus, the lenticular nucleus and the caudate nucleus. In the peduncle the infiltration of the vessels and the hyperæmia were more marked in the grey substance than in the white matter and the infiltration of lymphocytes and plasma cells was confined much more to the walls of the veins than to those of the arteries. The cells of the substantia nigra were not particularly affected in spite of the fact that there were more capillaries filled with blood in this region.

On the other hand the same observations are applicable to the red nucleus. The capillary vessels of the corpora quadrigemina and of the grey matter of the peduncles and the promontory (protuberance) showed inflammatory reaction of the small vessels as intense as that in the cerebral cortex.

Very often the capillaries contained hæmatozoa few in number, but there were some of them in which nearly every red globule was parasitic (fig. 6). There were capillaries or precapillaries filled almost exclusively with lymphocytes, small or medium sized, arranged in one or two series. Less frequently these vessels were filled exclusively with polynuclears ending with one or two lymphocytes. In other vessels there was a mixture of lymphocytes and mononuclears and these can predominate.

The nodules which we have described in the white matter of the cerebral cortex are found more rarely in the peduncle. All the lesions which we have just noticed as being in the cerebral cortex, basal ganglia and peduncles are reduced to their simplest expression in the cerebellum when infiltration of the adventitia is exceptional, capillary congestion little marked and the number of hæmatozoa very limited.

We examined for the presence of hæmatozoa different glands such as the spleen, liver, suprarenal capsules, and ovaries, but we have not actually found the parasite of Laveran. There was certainly in the spleen and liver a great quantity of black pigment in the leucocytes and macrophagocytes which filled up the vessels, but I am sure that if there had been hæmatozoa in abundance as we had seen them in the nerve centres it would have been easy to make them evident. So we are obliged to admit that in this case the hæmatozoa localized their action principally to the nerve centres such as the brain, bulb and spinal cord, whilst the cerebellum was invaded to only a slight extent and the spinal ganglia still less.

Other observers before us, Laveran, Councilman, Marchiafava, Monti, Babès, Marinesco, and more recently Lafora. Margulis Cevetti and Babès have described the presence of hæmatozoa in the central nervous system ; but the inflammatory reaction of the vessels and the thrombus of lymphocytes are lesions which have been encountered exceptionally only. As to the inflammatory nodules which we may call by the name " malarial nodules," they are not mentioned in the writings of French, Italian, English or American authors. The essential cause of them seems to be a formative irritation due to the presence of hæmatozoa or their toxins. As to the mechanism of the myoclonic movements it is difficult to venture an exact opinion in the present state of our knowledge.

THE DOUBLE INNERVATION OF STRIATED MUSCLE.

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THE innervation of the striated musculature may be numbered amongst the many problems which have turned out to be far less simple than they appeared to be to an earlier generation of investigators. This is true whether we have regard to the structural or to the functional side of the problem.

It is the purpose of this brief communication to give an outline of certain contributions, from the morphological side, to our knowledge of the peripheral motor innervation of striped muscle, which are of interest, and possibly of great importance for the physiologist as well as the anatomist. Some of the facts and observations to be detailed have from time to time attracted attention under the heading of a "double innervation of striped muscle." Such a title, however, is ambiguous and unsatisfactory.

In the first place it obviously ignores the distinction between the motor and sensory innervation of the muscle tissue. But even if we substitute the expression "double motor innervation of striped muscle" there remains the objection that two very different conditions as regards the motor nerve supply of muscle have been recognized, either of which may well enough be brought under the category of a "double motor innervation."

(A) PLURISEGMENTAL INNERVATION.

It has long been known that single muscles are commonly supplied by motor nerve fibres from more than one segmental nerve. Indeed the cases of unisegmental nerve supply of a muscle are comparatively few in number. This fact has frequently been interpreted in terms of a corresponding plurisegmental, or polymeric, origin of the muscles so innervated. But the validity of the assumption that all such muscles are necessarily polymeric has not been established beyond doubt. Indeed in the case of the mammalian limb musculature, a derivation of the premuscle blastema from actual embryonic myotomes has not been proved. A definite and obvious origin of the limb muscles from the

myotomes lying opposite the site of origin of the limb buds has indeed been confidently alleged to occur in submammalian forms and it is very likely that the lack of evidence of a similar derivation in mammals is due to cænogenetic blurring of the outlines of the myogenetic process. However that may be, the fact remains that whether they are themselves polymeric or not, a large majority of the muscles of the body are plurisegmental as regards their nerve supply.

The question then arises how the terminals of the various nerve fibre groups supplying a muscle are distributed within the muscle. Are the nerve-fibres from each of the segmental nerves supplying the muscle distributed exclusively to individual muscle-fibres which belong morphologically to the corresponding body segment? Or is there a mutual interpenetration of segmental motor territories on the part of adjacent serial segmental nerves?

In considering these questions it must, however, be borne in mind that the histogenetic study of striped muscle has shown that individual muscle-fibres may be themselves composite segmentally. It has been shown that the myofibrillar differentiation by which the body of the muscle fibre is constituted takes place in a myoblastic syncytium. In the case of adjoining body segments this syncytium forms a continuum which connects contiguous myotomes across the intervening myosepta. Hence a muscle-fibre arising by myofibrillar differentiation in this syncytium may itself be strictly polymeric.

Agduhr (1916-1919) has recently attempted to answer some of the questions regarding the plurisegmental innervation of striped muscle which arise out of the facts outlined above. This author's investigation of the problem arose incidentally from his study of the physiological effects of conjoint and of separate stimulation of two segmental sources of nerve supply of one and the same muscle. Contrary to his expectation he had found that the force of contraction resulting from maximal stimulation of both nerves supplying a given muscle was substantially less than the sum of the contraction force exerted by the muscle when its two sources of nerve supply were separately subjected to maximal stimulation. This phenomenon he was constrained to interpret in terms of an overlapping of the innervation regions of the separate nerves within the muscle. He found also that the region of a muscle thus doubly innervated from two *segmental* nerves was much greater than the region doubly innervated by different *peripheral* nerve paths like the median and ulnar nerves. In other words, the segmental overlap was considerably greater than that of the peripheral nerves, just as

has been found in the case of sensory overlapping. The extensive motor segmental overlap seemed to the author to indicate that a large number of the individual muscle-fibres possess a double, plurisegmental innervation. This question he proceeded to examine by a series of experimental observations.

By the employment of various forms of metallic impregnation (gold chloride as well as his own modification of Bielshowsky's technique) he was enabled to detect and to discriminate between the products of post-operative neuraxon degenerations of varying duration. The following experimental procedure gave instructive results: in a cat the author resected, at different periods, the first thoracic nerve root (ninety hours before the death of the animal) and the seventh cervical nerve root (fifty-eight hours before death). On killing the animal, after the lapse of the period indicated, the M. flexor sublimis digitorum, whose nerve supply is from the seventh and eighth cervical and the first thoracic nerve, was treated by an impregnation method to bring out the motor nerves and their terminations. The three categories of nerve structure corresponding to the three segmental nerves supplying the muscle could be readily distinguished. The endings of the fibres of the eighth cervical nerve were normal. Those of the first thoracic nerve were distinguishable by their more advanced, and those of the seventh cervical nerve by their less advanced degenerative characters. By these criteria it was possible to recognize that many of the individual muscle-fibres were certainly innervated by two successive segmental nerves.

It is well known that one and the same muscle-fibre often possesses two or three motor end-plates. It is therefore interesting to note that this author never came across a muscle-fibre (in the special degeneration preparations) which showed more than one motor end-plate of the same phase as regards degeneration. He will not venture to affirm it as invariable, but suggests that where a striped muscle-fibre has more than one motor end-plate these belong to different segmental nerves.

As against this view, it must be noted that both Floresco (1904) and Cavalié (1901) have definitely described motor nerve-fibres giving off terminal filaments to two or three motor end plaques situated in some cases on one and the same muscle-fibre and in others on neighbouring muscle-fibres or on an adjoining neuro-muscular spindle.

Although these facts would appear to be easily adaptable to the theory of an accurate correspondence between nerve and muscle segment, Agduhr does not favour the view that the plurisegmentally

innervated muscle-fibres he has observed do themselves actually originate from several myotomes. This he regards as unlikely on account of the fact that, as a rule, the end-plates belonging to the different segmental nerves are not placed so far apart on the muscle-fibre as might be expected on such an hypothesis, but, on the contrary, are rather close together. Also he frequently found two closely adjacent end-plates innervated by the seventh cervical and first thoracic to the exclusion of eighth cervical. In his second (1919) paper on the same subject the author has considerably extended his experimental observations confirming his previous conclusions. In order to meet criticism of his earlier work to the effect that the periods he had allowed for degeneration were not such as to exclude mere differences in the degenerative reaction to section of different fibres, Agduhr substantially increased the periods of differential degeneration, and his figures convincingly support the validity of the claim to recognize fibres of different degeneration phase. Figs. 1 and 3 of his paper very clearly illustrate bi- and tri-segmental innervation respectively of individual muscle-fibres.

B.—"Accessory" System of Motor Fibres of Alleged Sympathetic Origin.

An entirely different type of "double-motor innervation of striped muscle" may next be considered. This double innervation is constituted by the presence in the various skeletal muscles so far examined, of non-myelinated motor nerve-fibres which are alleged to be quite independent of the ordinary myelinated motor nerve-fibres not only in structural connexion but in origin and source. These "accessory" motor nerve-fibres sometimes terminate in the same motor end-plates in which the terminals of the ordinary motor nerve-fibres end. But they frequently end in accessory, independent, motor end organs of characteristically smaller size.

Various observers have concluded that these accessory nerve-fibres are of sympathetic origin. This interpretation seemed at first to rest upon slender and unconvincing evidence. But the more recent observations, more especially those based upon the appearances met with as the result of experimental nerve degeneration, seem to establish beyond reasonable doubt at least the independence of the accessory fibres from the system of myelinated fibres which constitutes the hitherto accepted motor supply of the muscle.

The idea of the existence of an accessory, sympathetic source of

motor supply to striped muscle is not novel, although it is only within the last decade that the evidence offered has become strong enough to claim serious consideration.

So far back as 1882 Bremer recorded the discovery, in the frog and the lizard, of fine non-medullated nerve-fibres entering the motor end-plates which form the terminal apparatus of the ordinary medullated motor nerve-fibres of striped muscle. Bremer (1882) distinguished in striated muscle nerve-fibres of three orders: (1) coarse myelinated, (2) fine myelinated, and (3) unmyelinated. He held, however, that the third were connected with the second, though not with the first.

It was not until further advances had been made in neuro-histological technique, as well as in the development and application of the neurone theory, that any significant progress was made in the recognition and discrimination of different categories of nerve-fibres innervating striped muscle.

The introduction of the *intra vitam* methylene blue method of Ehrlich led to many researches on both the sensory and motor innervation of muscle in the late 'eighties and early 'nineties. But neither Gerlach (1889), Dogiel (1891), nor Retzius (1892), all of whom employed this method, has recorded any evidence of specific distinction among the motor innervating nerve-fibres. Nor has Kallius (1896), in his review of this area of investigation, anything further to record in this direction.

Not till we reach the earlier years of the present century do we find further evidence to confirm, and greatly to extend, Bremer's early observations. This newer evidence has been the result of the application of various methods of technique.

These have included modifications of the familiar and well-tried gold chloride method; the newer reduced silver methods of Ramón y Cajal, and, especially, that of Bielschowsky in one or other modification.

Perroncito (1901) described and figured in the lizard unmyelinated nerve-fibres in striated muscle connected with the ordinary motor end-plates but otherwise distinct from the medullated nerve-fibres which end in these plates. Neither the description nor the figures, however, would suffice to differentiate them from the fine, unmyelinated, "ultraterminal" filaments as described and figured by Ruffini (and Apathy) (1900). These ultraterminal fibres are merely unmyelinated filamentous continuations of the neurofibrillar apparatus of an ordinary motor end-plate. Boeke's (1909) more recent investigation of the

development of motor end-plates serves completely to explain in this sense this " ultraterminal " relationship.

In a later paper Perroncito (1902) deals further with the appearance of unmyelinated fibres in muscle. Several instances are there given and illustrated of fine non-medullated fibres accompanying a medullated fibre and ending in the same motor plaques with the branches of the latter. But there is no evidence that the fine fibre shown, e.g., in his fig. 3, Plate I, is not a non-medullated collateral, similar to that actually shown springing from a medullated fibre in his fig. 6, Plate I. Figs. 1, 2, 4 and 5 all show fine non-medullated fibres some of which are obviously collaterals, whilst all may either be collaterals or ultraterminal filaments. Fig. 2 shows a non-myelinated fibre reaching its destination, a motor end-plate, from a different direction to that of the medullated fibre going to the same plate. Probably this is not a collateral from the latter, but there is nothing to show that it may not be an ultraterminal fibre like those illustrated in the text-figures of the author's earlier paper.

Although Perroncito suggests a sympathetic character for the unmyelinated filaments the only evidence adduced is an alleged connection in a few cases with a perivascular nerve plexus. It is clear that neither in the case of the non-medullated collaterals nor in that of the ultraterminal filaments can there be any question of a sympathetic origin or nature of the fibres concerned.

Grabower (1902) contributes the result of his observations on human muscle. He could not recognize any clear-cut distinction of nerve-fibre types, there being all grades from very fine pale fibres to thick medullated ones. He only rarely met with wholly unmyelinated fibres which could be traced as independent fibres for any long distance. Usually they were fibres resulting from the branching of medullated fibres. These often accompanied the latter in a common Henle's sheath, but might end independently.

Gemelli's (1905) observations confirmed Perroncito's, but by showing a definite continuity in the motor end-plates between the arborizing filaments of the unmyelinated fibre and the ramifications of the axon of the medullated fibre, they tended to establish the " ultraterminal " nature of that form of unmyelinated fibre.

Botezat (1906) described a double innervation of striped muscle fibre in birds by both medullated and non-medullated fibres. This author directed attention to the differences between, and the apparent independence, of the two systems. He pointed out that the endings

of the non-medullated fibres were unlike any known sensory ending and resembled the motor, but he did not otherwise determine either their character or their derivation.

Thus far, then, no satisfactory proof of a dual system of innervating motor-fibres had been provided. The appearances which had given rise to the suggestion of such a duality of innervation were probably for the most part to be explained in a quite different and much less remarkable fashion. Nevertheless the suggestion of an anatomical basis for a dual innervation was immediately caught up by some physiologists as providing an hypothesis which some of the physiological phenomena of muscular activity seemed to demand.

Floresco (1904) resected on one side the cervical sympathetic but found no motor atrophy or asymmetry of facial muscles and the motor end-plaques were found to be unaffected in the masseter muscle.

Mosso (1904) quotes Bottazzi's (1897 and 1901) view that the sarcoplasm is the contractile substance which is active in the slow tonic phase of muscular activity, whilst the anisotropic substance is involved in the rapid form of contraction. Mosso, however, denies that the prevalence of tonus in muscle is proportional to its richness in sarcoplasm as Bottazzi was disposed to believe.

It is chiefly the work of Boeke from 1909 onwards which has led to the wide, though by no means universal, acceptance of the evidence for a double motor innervation of striped muscle in the sense now under consideration. In the course of an investigation published in 1909, on the development of the motor end-plates of invertebrates, Boeke was led to recognize the occurrence in muscle of a system of fine non-myelinated fibres which appeared to him to be quite independent of the ordinary myelinated fibres. These non-medullated fibres showed characteristic terminations in the shape of fine end-rings, loops or nets. They were sometimes embedded in the sarcoplasm of the end-plate connected with an ordinary myelinated motor-fibre, but in other cases they ended in small independent end-plates on the muscle-fibres. Boeke laid stress upon their hypolemmal position and their often intimate association with the ordinary motor end-plates as witnessing to their centrifugal and quasi-motor function. He named these non-myelinated fibres "accessory" fibres, and their terminals "accessory" nerve-endings.

In a more extended paper in 1911 and again in 1913, he compared his observations on the "accessory" fibres with the descriptions given by previous observers of non-myelinated filaments noticed by them in

striped muscle. He concludes that for the most part these latter were either simply non-medullated collaterals or similar ultraterminal prolongations of ordinary motor-fibres and were, therefore, not the same as the "accessory" system of fibres discovered by him. He gave definite expression to the opinion (1913) that the "accessory" system of fibres could hardly be other than sympathetic or autonomic in character. Whether they were concerned with the conduction of trophic stimuli or with the tonic innervation of the striated muscle, he left to the physiologists to decide. In this connection accordingly he made reference to the work of Pekelharing and van Hoogenhuyze (1910), who had claimed to establish the occurrence in muscle of two distinct chemical processes, one characteristic of tonic activity and the other of ordinary contraction. He also referred to the support given by Mosso (1904) to the theory of double innervation from the physiological side, and to the more recent work of de Boer (1915) in van Rynberk's Laboratory, where this author claimed to have established experimentally in the case of the frog's muscle that the tonic innervation of muscle is conducted from the spinal cord not along the spinal motor-fibres but along fibres from the sympathetic chain, which reach the mixed nerves through the communicating rami.

In the paper just referred to, de Boer claims to have found that the tonus of most skeletal muscles is carried by the thoracic autonomic system. De Boer also refers to the experiments of Ken Kure, Tohei Hiramatsu and Hachiro Naito which appeared to show that section of the phrenic nerve did not abolish tonus of the diaphragm though it paralysed it; on the other hand, section of the splanchnic nerves produced definite atony of the diaphragm. Following up the physiological side of this question, Dusser de Barenne (1917) was able partially to confirm de Boer's work. He found, however, that the disappearance of tonus of the muscles of the lower limb, after extirpation of the abdominal sympathetic, was not total but partial—hypotony, not atony, was the result—and further, the hypotony gradually disappeared. He concludes, therefore, contrary to de Boer, that the greater part of the muscular tonus is after all conducted by cerebrospinal fibres. He is unable to decide the question whether that part of the tonus which disappears on the production of an acute sympathetic lesion is actually due to the cutting out of autonomic fibres or not. Kuno, working in Starling's Laboratory in University College, London, did not find any diminution of tonus after extirpation of the sympathetic or after section of the rami communicantes.

In a later contribution, Dusser de Barenne (1919) again attacks the physiological problem of the peripheral path for tonic nerve impulses. Here he brings further proof, as against de Boer, that the sympathetic fibres have nothing to do with the transmission of "mechanical muscle tonus." On the other hand, he fully concurs in Boeke's conclusions respecting the sympathetic, centrifugally conducting, character of Boeke's "accessory" fibres, and goes on to suggest that although they can have nothing to do with the propagation of the stimuli of "mechanical" tonus, they may very well be the pathway along which the "chemical" tonus of striped muscle is influenced by the central nervous system.

On the whole it may still be said that the physiological evidence on this question is of a rather equivocal character.

But the morphological evidence not only in favour of the independent existence of Boeke's "accessory" system of fibres, but in favour of its sympathetic derivation, was later supplemented by various observations of the results of experiments in nerve degeneration. Boeke's own experimental results in this direction are embodied in his important "Studien zur Nervenregeneration," I and II, in the *Transactions of the Royal Academy of Sciences of Amsterdam*, in 1916-1917. The nature of the evidence thus obtained may be indicated as follows: In one series of experiments the muscles of the eyeball were investigated. The work of Sherrington, and of Sherrington and Tozer, had shown that the eye muscle nerves in their course from the brain to the muscles form the pathway for all the ordinary muscle-innervating fibres, sensory as well as motor. In a number of experiments Boeke (1917) resected one or other of the oculo-motor nerves close to its origin from the brain. When such an animal was killed a few days (three to five) after the experiment, and a study of the ocular muscles carried out with the aid of the Bielschowsky method, it was found, as was to be expected, that all the medullated nerve-fibres were undergoing degeneration. This was also the case with their associated end-organs. The degenerated fibres and terminals no longer showed the Bielschowsky silver reaction, and this served to bring out with almost diagrammatic clearness the system of non-medullated "accessory" fibres and their hypolemmal endings in the muscle. This system of fine non-medullated nerve-fibres was still so well represented in the muscle, that apparently each muscle-fibre possessed at least one "accessory" platelet. In one of his accounts of these results Boeke suggests that they can only be explained on the hypo-

thesis that these undegenerated, non-medullated fibres are transferred to the eye-muscle nerves by way of the sympathetic branch, which reaches the orbit from the carotid plexus. But his own further experimental observations show that the conditions in this special case of the eye-muscles are not so simple and definite as the account summarized above would suggest. In a series of further experiments Boeke found that when a longer period was allowed to elapse, e.g., three weeks, between the experimental nerve section and the killing of the animal, the greater number—though still not all—of the non-medullated fibres were found to have also undergone degeneration and to have disappeared from the picture. The only explanation offered is that non-medullated fibres resist degeneration after section longer than medullated. On the basis of these facts Boeke suggests that the tardily degenerating non-medullated fibres belong to the cranial autonomic system of Langley included in the eye-muscle nerve-trunks, whilst the other non-medullated fibres—fewer in number—which show no degeneration after a prolonged period following section of the nerve trunk near the brain, are those which have been transferred from the sympathetic to the eye-muscle nerve during its course peripherally.

The attempt to test this result in other cases by extirpation of the superior cervical ganglion showed that this lesion did not lead to disappearance of the system of accessory non-medullated fibres in the eye-muscles, although Boeke records his impression that they were less abundant than in the series with intact superior cervical ganglion. Boeke himself summarizes his conclusion from these facts and observations in a statement which may be translated as follows: "There is present in the eye-muscles, in addition to the motor and sensory nerves, a system of non-medullated fibres independent of these and provided with small hypolemmal end-platelets upon the muscle-fibres. The great majority of these fibres run in the trunks of the motor-nerves of the ocular muscles and belong to Langley's cranial autonomic system; only a small part of the fibres in question belong to the sympathetic in the narrower sense." (1917, p. 18.)

It seems to the writer that Boeke's interpretation is open to grave criticism in more than one direction. Much is made to depend upon the validity of a distinction founded upon mere difference of degeneration time of two categories of fibres. His clearest demonstration of the non-medullated fibres in the ocular muscles is provided by material in which, as it turns out, most of these fibres have already, according to his interpretation, been actually severed from their trophic centres.

They have, therefore, already entered on the career of degeneration. Can one, in these circumstances, be perfectly confident that very thin sheaths of myelin have not already suffered? Again, it is possible that Boeke may be right in identifying these tardily degenerating non-medullated fibres within the muscle with Langley's cranial autonomic fibres, but if they are they ought to be post-ganglionic axones of distribution. Where, then, does the synapse occur in the case, say, of trochlear fibres for the superior oblique muscle? Why, too, it may be asked, should degeneration occur at all if only pre-ganglionic fibres in the nerve-trunk close to the brain have been cut? These latter should of course be fine medullated fibres, if they represent pre-ganglionic elements of Langley's cranial autonomic system.

Further, Boeke does not definitely claim to have shown that the particular non-medullated fibres in the eye-muscles, which he alleges to persist permanently after section of the main nerve-trunk, and regards as sympathetic, have been certainly traced to hypolemmal end-organs. In fact, he admits that he was unable to find degenerated fibres and end-plates in cases where the superior cervical ganglion had been extirpated but the cerebral nerves left intact. There is, therefore, no stringent proof that true sympathetic fibres in the case of the eye-muscles do actually innervate accessory end-platelets in muscle-fibres.

It is strange that in a later paper published by Boeke and Dusser de Barenne in 1919, where the results of the above experiments on the eye-muscle nerves are again referred to, no reference whatever is made to the belated degeneration of the majority of the non-medullated fibres after experimental section. The unqualified statement is made that "the accessory non-medullated fibres, however, and their end-organs on the muscle-fibres remained unaltered, which could only be explained by admitting that they are transferred to the eye-muscle nerves by way of the sympathetic branch," &c. The discrimination introduced two years before between two different groups of non-medullated fibres held to be of diverse origin is now altogether ignored. Fortunately for Boeke's general interpretation the joint paper referred to furnishes other experimental evidence which appears much less open to criticism than that provided by the case of the eye-muscles.

The facts are these: In a cat the anterior and posterior roots of the sixth to ninth thoracic nerves inclusive were resected and the corresponding spinal ganglia were also extirpated. After the lapse of a period of one month the animal was killed and the condition as regards innervation of the muscles of the seventh intercostal space was

then investigated. The result was that while not a single medullated nerve-fibre remained intact and the motor end-plates in connection with them had disappeared there were still present fine bundles of non-medullated fibres connected with the muscle-fibres by means of small and delicate end-organs, end-rings, loops or end-nets. These, as figured in the paper, are precisely like those so abundantly illustrated in previous publications regarding the accessory fibres, and there can be no reasonable doubt of their identity with them.

That the end-organs of such non-medullated nerve-fibres are actually hypolemmal and therefore almost certainly motor in character, is supported by quite a number of Boeke's figures from his various papers, especially those showing profile views of the end-organs in question, e.g., "Studien zur Nervenregeneration," II, 1917, plate 1, fig. 7. The hypolemmal position, to which great importance must be attached, is also convincingly testified to by fig. 2 in the short paper by Boeke (1910), on pp. 481-4 of the *Anatomischer Anzeiger*, Bd. 35. In this figure we have an "accessory" terminal fibre ending in an ordinary motor plate along with the more extensive fibrillar expansion of an ordinary motor-nerve termination. Here, within the end-organ itself, a branch of the "accessory" terminal is seen to pass *under cover of* the fibrillar network of the ordinary motor ending, and therefore could not possibly be other than hypolemmal if honestly and accurately delineated.

In the proceedings of the same meeting of the Royal Academy of Sciences at Amsterdam, at which the paper by Boeke and Dusser de Barenne was presented, there also appeared a paper by E. Agduhr (1919) bearing the title, "Are the Cross-striated Muscle-fibres of the Extremities also innervated sympathetically?" This author investigated muscles of the extremities, especially the interossei muscles in the cat. He performed two different series of experiments. In one series (two cats) he extirpated the ganglion stellatum of one side. On killing the animal after the lapse of a few days he succeeded in finding in the muscle the remains of degenerated non-medullated nerve-fibres. The other series of experiments is more fully reported. They resembled those of Boeke and Dusser de Barenne. He resected the last four cervical and the first two thoracic nerves, in each case at a point between the spinal ganglion and the connection of the nerve trunk with the white ramus communicans. The animals were killed from five to ten days after the operation. On investigating the interossei muscles by the Bielschowśky method it was clear that all the myelinated fibres, both motor and sensory, had undergone degeneration. On the other

hand, the investigator found quite a number of intact non-medullated fibres, and he was able to follow a large number of these to their terminal organs. These were situated partly on ordinary striped muscle-fibres and partly on muscle-fibres in muscle spindles. Fig. 2 of his paper illustrates two ordinary motor end-plates, both degenerated, and situated quite near one another on a muscle-fibre. In one of these degenerated end-plates is seen the undegenerated termination of one of Boeke's "accessory" fibres. Fig. 4, on the other hand, shows in close proximity to one another, on the same nerve-fibre, a degenerated end-plate and an undegenerated one pertaining to the terminal ramifications of a non-medullated, "accessory," "sympathetic" nerve-fibre which are clearly visible in it. Agduhr's results accordingly serve to corroborate in all essentials the observations of Boeke on the independent existence of an accessory system of nerve-fibres. It is therefore difficult, if not impossible, to avoid the conclusion drawn by Boeke and supported by Agduhr and others from the results of what would appear to be crucial experiments, that these accessory fibres are sympathetic in origin and hypolemmal in their mode of termination. These relationships, if admitted, would seem to indicate a centrifugal conduction along these fibre paths of nerve impulses, presumably of motor and possibly of tonic contractile character.

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Proceedings of the Section of Neurology of the Royal Society of Medicine.

Held March 10, 1921.

Chairman—Dr. ERNEST S. REYNOLDS.

Discussion held in connection with the Section of Ophthalmology on Ocular Palsies.

The discussion was opened by GORDON HOLMES, C.M.G., M.D., and LESLIE PATON, F.R.C.S.

The addresses of the openers appear in full in the *British Journal of Ophthalmology*, June, 1921, vol. v, pp. 241 and 250.

April 14, 1921.

Dr. RIDDOCH described certain nociceptive reflexes of the upper limb (this paper will appear in a subsequent number of *Brain*).

Dr. BROOKE demonstrated a model of the brain and spinal cord.

May 12, 1921.

A paper by Prof. MARINESCO was read on "A Case of Myoclonic Encephalo-myelitis of Malarial Origin." This paper appears on p. 223 of the present number.

Notices of Recent Publications.

Klinische und anatomische Beiträge zur Pathologie des Gehirns. Von Professor Dr. S. E. Henschen.

Fünfter Teil. "Ueber Aphasie, Amusie und Akalkulie," S. 216, mit 15 Tafeln.

Sechster Teil. "Ueber sensorische Aphasie," S. 231, mit 11 Tafeln.

Stockholm: Nordiska Bokhandeln. 1920.

In 1912, Professor Henschen reached his sixty-fifth year and retired from the post of Director of the Medical Clinic in Stockholm. He then devoted himself to the mass of material and observations which he had collected during his active life, and published three authoritative monographs on the auditory, the visual and the olfactory centres. Like all who have busied themselves with cerebral localization, he was led to consider the problem of aphasia, a riddle which has occupied a prominent place in medicine for nearly a hundred and twenty years. His profound knowledge of cerebral anatomy revealed to him the shaky ground on which much of the current teaching was based, and he determined to tabulate and publish in abstract every case of these disorders of speech in which there had been a sufficient anatomical examination. These two volumes form a portion of this colossal task.

The arrangement is throughout based on the same principles. The clinical manifestations are set out usually under the headings of word-deafness, word-blindness, motor aphasia, agraphia, amnesia, paraphasia and accessory symptoms. The nature and situation of the lesion is given as nearly as possible and in certain instances a drawing of the brain is to be found on one of the many tables. Then follows a short abstract of each case under the name of the observer, numbered consecutively. At the end of each section is a short general summary of the conclusions which emerge from such revision.

The first of these volumes begins with a short re-statement of the author's own personal contributions to the case-material of aphasia; he then passes on consider amnesia and "akalkulie," of which he has collected 304 examples. As the result of this analysis he arrives at the conclusion that comprehension of music is predominantly due to the activity of the polar portion of the temporal lobe. When this centre on the left side is destroyed, that on the right can occasionally assume the lost function, but this is by no means invariable. He complains that the data for a similar examination of lesions responsible for "akalkulie" are unsatisfactory, because it is often

impossible to decide whether numbers could be written and understood or not. A + or o on the table does not give an exact expression of the facts; for the patient may be able to add but not to multiply. The author considers, however, that the mechanism for reckoning is separable from that for speech and music, and rests on a different anatomical substratum.

Fasciculus VI opens with a collection of cases of temporal and so-called transcortical aphasia, and then each group is considered separately. Henschen concludes that auditory speech is lost without recall on destruction of T.1. It cannot be replaced by the right hemisphere, which shows its inferiority to the left, exactly as is the case with F.3 in motor speech. But the right hemisphere is responsible for primitive automatic echo-speech and particularly for emotional expression.

As the result of his analysis of cases of so-called transcortical sensory aphasia, he comes to the conclusion that this form stands on a sound basis. The name "transcortical" signifies that the disturbance lies on the other side of the cortical areas for the formation of speech, and that the lesion is not situated in the so-called speech centres.

Then follows a systematic consideration of "angular," "parietal" and "occipital" aphasia, together with the combined forms.

The author comes to the final conclusion that investigation of word-deafness and word-blindness points to a strict localization of the forms of aphasia and to a close organization in the structure of the brain of the elements of speech, including the psychical functions. There is an enormous adaptive power in the brain cells which can be brought out as the result of suitable education and training; the right half of the brain is a colossal uncultivated field with innumerable and little educated cells, and this virgin ground may possibly be made to yield a full crop, although now it stands on a low level of development.

Professor Henschen promises us another volume on "Motor Aphasia," following the same lines, and all who are interested in cerebral pathology must sincerely hope that he may be spared to finish this incredible labour. For however much we may differ from the conclusions which he draws from this anatomical material, it is of the greatest importance that the recorded facts should be collected and analysed by so distinguished an anatomist. We are all anxious to know the site of the various lesions that can disturb speech, and it is often possible to see through the insufficient clinical records the main factors in the disorder. Round and round like a stage army moves the procession; the clinical appearances are identical, but each fresh group of spectators views them with new eyes and with different preconceptions. But it is often possible to recognize through the hazy reports and different classification of previous generations some salient point which indicates the identity of some past case with one under examination to-day. It is therefore of fundamental importance to know the site and nature of the anatomical lesion which produces such a condition, and we cannot be sufficiently grateful to the author of these monographs for this wonderful collection of data which can only be utilized to the full by our successors.

Anatomie du Système Nerveux. Première partie. "Les appareils nerveux de l'olfaction, de la vision, de la sensibilité générale, du goût." By Dr. CORNELIS WINKLER. 1918. Pp. 435.

In this volume an attempt has been made to describe fully certain of the organs of special sense in relation to their connections in the central nervous system. The arrangement is one to which students of neurology are now well accustomed, and it is without doubt the most useful method of presenting the anatomy of the nervous system to the clinician.

The olfactory, visual, and taste organs and the apparatus of cutaneous sensibility alone are dealt with in this volume, the apparatus of the internal ear and its connections with the central nervous system being left for a later volume. This arrangement is, no doubt, necessitated by the close relation between the vestibular nerve and the lower motor paths, but it leaves the volume somewhat incomplete as a description of the sensory organs of the human body.

The book gives a fairly full historical résumé of the progress of knowledge on the subjects dealt with, and in many places the author's own experiments and those of other neurologists of the Dutch school are given in some detail. Dogmatic statements are avoided and the reasons for the conclusions arrived at are fully stated.

The French translation has been admirably carried out by Dr. Victor Willem. The illustrations, in which for the most part the Latin terminology is employed, are numerous and clear.

The book is one which will repay serious study as a whole, and is of considerable value as a work of reference.

Einführung in die Lehre vom Bau und den Verrichtungen des Nervensystems. By the late Professor Dr. LUDWIG EDINGER. Third Edition, 1921. S. 233. Edited by Professor Dr. KURT GOLDSTEIN and Professor Dr. A. WALLENBERG.

The second edition of this book, published in 1912, has been out of print for some years, and a third edition was urgently called for. The editors have, however, contented themselves for the present with re-editing the book in its previous form, leaving to a fourth edition the alterations which have been necessitated by recent progress in our knowledge.

The present volume is a useful introduction to the anatomy and physiology of the nervous system. Its 176 illustrations and diagrams are well conceived and clearly reproduced; the text is not only brief, and to the point, but avoids to an unusual extent the error of giving dogmatic statements on unsettled points which is so common in small books on this subject. The absence of an index reduces to some extent the value of the book, and we hope this may be rectified in the next edition.

Addresses on Psycho-Analysis. By J. J. PUTNAM, M.D., Emeritus Professor of Neurology, Harvard University. With a Preface by SIGM. FREUD, M.D., LL.D. Pp. 470. London: The International Psycho-Analytical Press, 1921.

Psycho-Analysis and the War Neuroses. By Drs. S. FERENCZI (Budapest), KARL ABRAHAM (Berlin), ERNST SIMMEL (Berlin), and ERNEST JONES (London). Introduction by Prof. SIGM. FREUD (Vienna). Pp. 59. London: The International Psycho-Analytical Press, 1921.

The urgent necessity for dealing therapeutically with large numbers of patients suffering from mental illnesses in the recent War was the means of widening interest in psychological methods. The claims of the various schools of clinical psychology were investigated, and it was soon realized that Freud in his work had done much more than originate his sexual theory of the neuroses His conceptions of mental mechanisms underlying the production of symptoms in states of emotional stress were perceived by many workers to be of more than theoretical interest. Psycho-analysis has gained an established place in neurology as a therapeutic measure of value under suitable conditions and in selected cases. At the same time many consider that its greatest value, however, in dealing with psychoneuroses is not as a method of treatment, but as a means of exploring unconscious mental processes for purposes of investigation.

The extension of interest in psycho-analytical methods in different countries has led to the establishment of an International Journal of Psycho-Analysis and an International Psycho-Analytical Library, both of which are edited by Dr. Ernest Jones. The volumes under review form the first two numbers of the library to be published in English.

In number one are republished a selection of the numerous papers upon psychological subjects written by the late Dr. J. J. Putnam in the last ten years of his life. Putnam, as Freud points out in the preface, was the first American to study psycho-analysis and, as a result of testing its value in practice, became an earnest although critical exponent of it. The book forms an interesting record of his views on the psychological doctrines of Freud, as well as those of Jung and Adler, and not the least of its attractions is the charming style in which it is written.

The second volume consists of four papers on psycho-analysis in relation to war neuroses. The first three were delivered by Austrian and German psychologists at the Fifth International Psycho-Analytical Congress at Budapest in 1918, and the fourth, written by Ernest Jones, is reprinted from the *Proceedings of the Royal Society of Medicine*, London. While all the writers admit the importance of the instinct for self-preservation in the production of war neuroses, some of them claim, and the others strongly suspect, that the real basic factors on one side are sexual in origin. Realizing, however,

the inadequacy of the original sexual hunger theory as an explanation of the traumatic neuroses of peace and war, they invoke the recently developed theory of narcissism or self-love. For them, as for Freud, danger to life is an etiological factor of insufficient strength in itself to lead to severe neurotic troubles, and assert as a belief that extensive mental analysis would bring to light underlying sexual influences of primary importance. But it is by adopting an attitude of this kind, which is unsupported by convincing evidence, that the followers of Freud do much to bring into discredit his theories and methods, and to obscure what is admittedly of great value in them.

Lunacy in India. By A. W. OVERBECK-WRIGHT. Pp. 406. London: Baillière, Tindall and Cox, 1921.

The objects of this book are stated by the author to be threefold: "to summarize the condition of lunatics in India and the means available for treating them; to emphasize the importance of toxæmias as etiological factors in the production of a very large proportion of such cases . . . . and lastly, to place on record views to which a wide and varied experience of the East, spread over more than nineteen years, has given rise." Unfortunately the author has attempted to write a complete work on Mental Medicine, and has included much that can be found in ordinary text-books. But the illustrative cases are taken from his own experience in the East, and many of them contain fascinating suggestions for further investigation. His comments throw a valuable light on the customs of the people with whom he has had to deal, but they are too short, and the author's diffidence has robbed us of much interesting information. If this book comes to a further edition, we should strongly recommend that the more specific aspects of the subject should be given greater space at the expense of the more commonplace generalizations.

Diseases of the Nervous System. By SMITH ELY JELLIFFE, M.D., Ph.D., and WILLIAM A. WHITE, M.D. Third Edition, revised, rewritten and enlarged. Pp. 1,018. Illustrated with 470 Engravings and 12 Plates. Philadelphia and New York: Lea and Febiger, 1919.

This well-known text-book has been largely re-written. The first chapter is concerned with methods of examination which even include a few words on the technique of psycho-analysis. Then follow 160 pages devoted to vegetative and visceral neurology together with the endocrinopathies. Part II deals with the sensori-motor systems; affections of the cranial and peripheral nerves, lesions of the spinal cord, brain-stem, cerebellum and cerebrum are then treated systematically in consecutive chapters, and a remarkable amount of information has been gathered into a small compass. The third portion of the book is devoted to the neuroses, psycho-neuroses, and psychoses, under

the heading of "Psychical or Symbolic Systems." The diagrams and figures are well reproduced, and we are glad to see that some of the more important monographs, from which the facts have been derived, are mentioned at the bottom of the page, so that the student can follow up points in which he is interested.

Mental Hospital Manual. By JOHN MACARTHUR, M.R.C.S., L.R.C.P. Pp. 215. London: Oxford Medical Press, 1921.

This is a straightforward account, in simple language, of the duties of an assistant medical officer and of his responsibilities both legal and medical. It gives in concise and handy form the sort of advice that would be offered to a junior on beginning work in an asylum. Copies are given of the various documents used in mental work, and they are carefully explained. This little book should be of considerable help to a young man contemplating the career of an A.M.O., or about to take the post of *locum tenens* in an asylum.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.